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TO: Ben Sackey **Location: 5b31/5c18** **Art Unit: 1626** **Wednesday, June 08, 2005** **Case Serial Number: 10/602617**	**From: Noble Jarrell** **Location: Biotech-Chem Library** **Rem 1B71** **Phone: 272-2556** **Noble.jarrell@uspto.gov**

Search Notes

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SEARCH REQUEST FORM

Scientific and Technical Information Center (1)

Requester's Full Name: BEN SACKEY Examiner #: 73484 Date: 6/7/05
Art Unit: 1626 Phone Number 30~~2~~-2-0704 Serial Number: 10/602,617
Mail Box and Bldg/Room Location: REM 5B3 Results Format Preferred (circle): PAPER DISK E-MAIL

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

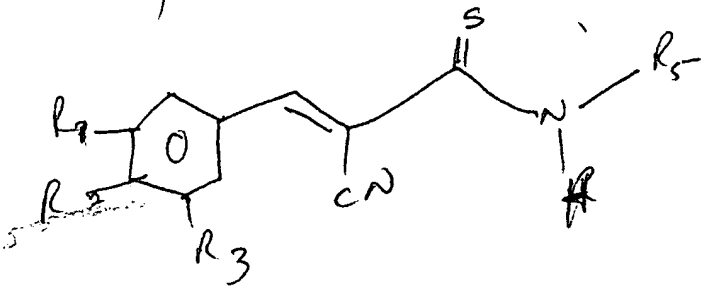
Title of Invention: Method of Compositions for Inhibiting Cell proliferative Disorders

Inventors (please provide full names): _____

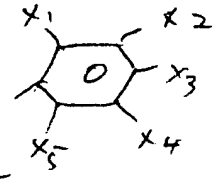
Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

A protein kinase inhibition Compositions Comprising



where R_5 is



substituents are as defined in the claim

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L1   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:1055200  HCAPLUS
ED   Entered STN:  09 Dec 2004
TI   Sheet computer, wearable computer, display device, fabrication methods,
     and electronic devices thereof
IN   Karaki,  Nobuo
PA   Seiko Epson Corporation, Japan
SO   U.S. Pat. Appl. Publ.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  H05K001-00
     ICS  H03K019-00
INCL 361749000
FAN.CNT 1
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004246684	A1	20041209	US 2004-797054	20040311 <--
PRAI	JP 2003-75039	A	20030319		
	JP 2003-433863	A	20031226		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 20040246684	ICM	H05K001-00
	ICS	H03K019-00
	INCL	361749000
US 2004246684	NCL	361/749.000
	ECLA	G06F001/10; G06F001/16; G06F001/16P; G06F001/16P5; H01L023/498J <--

AB It is an object of the present invention to propose a sheet computer that eliminates the drawback in operational speed caused by clock delays of a system clock and that is capable of high speed operation. In order to achieve this object, in the sheet computer of the present invention, a display circuit and peripheral circuits connected to the display circuit are fabricated on the same substratum and the peripheral circuits constitute an asynchronous system without global clocking. In the asynchronous system, processes constituting minimum function circuits perform mutual handshaking by channels and drive events actively or passively. The asynchronous system does not use global clocking and it is therefore possible to implement lower power consumption and a higher operational speed.

L1 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:534888 HCAPLUS
DN 129:156926
ED Entered STN: 24 Aug 1998
TI Methods and compositions using receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders, and inhibitor preparation
IN Chen, Hui; Gazit, Aviv; Hirth, Klaus Peter; Mann, Elaina; Shawver, Laura K.; Tsai, Jianming; Tang, Peng Cho
PA Sugen, Inc., USA; Yissum Research & Development Company of the Hebrew University of Jerusalem
SO U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 207,933, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A01N043-40
ICS C07D211-72
INCL 514352000
CC 1-6 (Pharmacology)
Section cross-reference(s): 25, 28, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5789427	A	19980804	US 1995-399967	19950307 <--
	US 5773476	A	19980630	US 1995-486775	19950607
	US 6596878	B2	20030722	US 2001-953933	20010918 <--
	US 2004242684	A1	20041202	US 2003-602617	20030625
PRAI	US 1994-207933	B2	19940307		
	US 1995-399967	A1	19950307		
	US 1995-486775	A1	19950607		
	US 1998-70318	B1	19980429		
	US 2000-722149	B1	20001122		
	US 2001-953933	A3	20010918		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5789427	ICM	A01N043-40
	ICS	C07D211-72
	INCL	514352000
US 5789427	NCL	514/352.000; 514/357.000; 546/304.000; 546/330.000

	ECLA	A61K031/245+A; A61K031/277; A61K031/415+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C255/66; C07C311/27; C07C317/46; C07C327/44; C07D241/52B1; C07D241/52B5 <--
US 5773476	NCL	514/620.000; 514/618.000; 514/619.000; 564/162.000; 564/164.000; 564/165.000; 564/167.000; 564/168.000; 564/170.000
	ECLA	C07C229/60; C07C255/41; C07C255/66
US 6596878	NCL	548/371.700; 558/402.000; 558/404.000
	ECLA	A61K031/245+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C255/66; C07C311/27; C07C317/46; C07C327/44; C07D241/52B1; C07D241/52B5; A61K031/277; A61K031/415+A <--
US 2004242684	NCL	514/521.000; 558/401.000
	ECLA	A61K031/245+A; A61K031/277; A61K031/415+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C255/66; C07C311/27; C07C317/46; C07C327/44; C07D241/52B1; C07D241/52B5

OS MARPAT 129:156926

AB The invention concerns compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders, e.g. cancers characterized by over-activity or inappropriate activity HER2 or EGFR.

ST receptor tyrosine kinase inhibitor prepn antiproliferative; antitumor receptor tyrosine kinase inhibitor prepn; HER2 EGFR kinase inhibitor antiproliferative antitumor

IT Animal cell line
(A431; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Ovary, neoplasm
Salivary gland
Salivary gland
Salivary gland
Stomach, neoplasm
Stomach, neoplasm
(adenocarcinoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Mammary gland
(carcinoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(chimeric, EGFR-HER2; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Intestine, neoplasm
Intestine, neoplasm
(colorectal, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Antitumor agents
(colorectal; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Uterus, neoplasm
Uterus, neoplasm
(endometrium, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Antitumor agents
(endometrium; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents

Antitumor agents
(gastric adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Neuroglia
(glioblastoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(glioblastoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Ovary, neoplasm
Stomach, neoplasm
(inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(mammary gland carcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(ovary adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(ovary; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Proliferation inhibition
(proliferation inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Cytotoxic agents
Drug delivery systems
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Epidermal growth factor receptors
Growth factor receptors
neu (receptor)
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Platelet-derived growth factor receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(salivary gland adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(stomach; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 1960-77-6P 5190-68-1P, 4-Chloroquinazoline 10537-86-7P, 3,5-Diisopropyl-4-hydroxybenzaldehyde 19181-54-5P 27389-84-0P 29634-62-6P 170449-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 93-91-4, Benzoyl acetone 94-02-0, Ethyl benzoyl acetate 98-16-8 99-40-1 100-46-9, Benzylamine, reactions 103-79-7, Phenyl acetone 105-34-0, Methyl cyanoacetate 108-42-9, 3-Chloroaniline 109-76-2, 1,3-Propanediamine 109-77-3, Malononitrile 109-80-8, 1,3-Propanedithiol 120-46-7, Dibenzoyl methane 123-54-6, 2,4-Pentanedione, reactions 139-85-5, 3,4-Dihydroxybenzaldehyde 480-96-6, Benzofuroxane 485-47-2, Ninhydrin 491-36-1, 4-Quinazolinone 579-07-7 868-54-2, Malononitrile dimer 1075-06-5, Phenyl glyoxal hydrate 1194-98-5, 2,5-Dihydroxybenzaldehyde 1620-98-0,

3,5-Di-tert-butyl-4-hydroxybenzaldehyde 2038-57-5, 3-Phenylpropylamine 2078-54-8, 2,6-Diisopropylphenol 2423-66-7 2941-78-8, 5-Methyl-2-aminobenzoic acid 3171-45-7 4389-45-1, 2-Amino-3-methylbenzoic acid 4518-10-9 5348-42-5, 4,5-Dichloro-1,2-phenylenediamine 5438-36-8, 5-Iodovanillin 7357-70-2 10412-93-8, N-Benzylcyanoacetamide 13790-39-1, 4-Chloro-6,7-dimethoxyquinazoline 14268-66-7, 3,4-Methylenedioxyaniline 16414-34-9, 3,4-Dihydroxy-5-bromobenzaldehyde 24522-30-3 27869-04-1 37463-94-8 40018-25-5, 2-Chlorobenzoylacetonitrile 54711-21-6 58421-79-7, 4-Chloro-6-methylquinazoline 74908-81-9 133550-33-1 138942-61-7 168835-79-8 170449-33-9 170449-34-0, 2-Pyridinesulfonylacetonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 79079-06-4, EGF receptor tyrosine kinase 127407-08-3, Receptor tyrosine kinase 137632-09-8, HER2 kinase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 101463-26-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 13494-38-7P 65224-45-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 555-60-2P 5023-53-0P 5784-78-1P 6639-86-7P 10537-47-0P 13297-17-1P 15034-21-6P 23190-84-3P 40114-83-8P 54259-09-5P 57859-60-6P 70071-08-8P 71896-95-2P 88404-44-8P 140674-76-6P 146871-70-7P 148741-30-4P 148741-31-5P 148741-32-6P 153436-53-4P 168835-82-3P 168835-87-8P 170448-89-2P 170448-90-5P 170448-91-6P 170448-92-7P 170449-00-0P 170449-12-4P 170449-13-5P 170449-14-6P 170449-15-7P 170449-16-8P 170449-17-9P 170449-18-0P 170449-19-1P 170449-20-4P 170449-21-5P 170449-22-6P 170449-23-7P 170449-24-8P 170449-25-9P 211298-73-6P 211298-75-8P 211298-81-6P 211298-83-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 65678-07-1 133550-41-1 170448-88-1 170448-95-0 170448-97-2 170448-98-3 170448-99-4 170449-02-2 170449-03-3 170449-04-4 170449-05-5 170449-06-6 170449-07-7 170449-08-8 170449-11-3 170449-26-0 170449-27-1 170449-28-2 170449-29-3 170449-30-6 186581-94-2 186581-95-3 186581-96-4 211299-44-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 15762-68-2P 19181-53-4P, 6-Methyl-4-quinazolinone 58421-80-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

RE.CNT 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD
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FOR DETAILS. <<<

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L4 ANSWER 1 OF 3 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-788780 [78] WPIX
DOC. NO. NON-CPI: N2004-621297
TITLE: Sheet computer for use in smart card, has electronic circuit and periphery circuit connected to display circuit, which are mounted on flexible medium.
DERWENT CLASS: T01 T04 U11 U14 V04

INVENTOR(S): KARAKI, N
PATENT ASSIGNEE(S): (SHIH) SEIKO EPSON CORP
COUNTRY COUNT: 2
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 2004303195	A	20041028	(200478)*		14	G06F001-16
US 2004246684	A1	20041209	(200481)			H05K001-00<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 2004303195	A	JP 2003-433863	20031226
US 2004246684	A1	US 2004-797054	20040311

PRIORITY APPLN. INFO: JP 2003-75039 20030319
INT. PATENT CLASSIF.:
MAIN: G06F001-16; H05K001-00
SECONDARY: G06F001-04; H03K019-00
BASIC ABSTRACT:
JP2004303195 A UPAB: 20041206
NOVELTY - The sheet computer used as an asynchronous system, comprises an electronic circuit and a periphery circuit connected to a display circuit, which are mounted on a flexible medium.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) wearable computer;
(2) display apparatus;
(3) electronic device;
(4) sheet computer manufacturing method;
(5) wearable computer manufacturing method; and
(6) display apparatus manufacturing method.
USE - In electronic device (claimed) such as smart card, electronic paper, and also implemented as wearable computer (claimed) and display apparatus (claimed) used in a variety of electronic devices.
ADVANTAGE - The reduction of operating speed by clock delay is eliminated and sheet computer of high-speed operational property is realized.
DESCRIPTION OF DRAWING(S) - The figure explains the communication between two asynchronous system. (Drawing includes non-English language text).
Dwg.1/9
FILE SEGMENT: EPI
FIELD AVAILABILITY: AB; GI
MANUAL CODES: EPI: T01-C07A; T01-K01; T04-K01; U11-D01A7; U14-K09; V04-Q02A3; V04-Q05; V04-R05D

L4 ANSWER 2 OF 3 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-174010 [17] WPIX
CROSS REFERENCE: 1995-336717 [43]; 1998-387069 [33]; 1998-465990 [40]; 2005-030032 [03]
DOC. NO. CPI: C2003-045395
TITLE: Use of protein kinase inhibitor compounds in compositions for treating cell proliferation disorders, especially cancers caused by inappropriate activity of HER-2 or EGFR.
DERWENT CLASS: B05
INVENTOR(S): CHEN, H; GAZIT, A; HIRTH, K P; LEVITZKI, A; MANN, E; SHAWVER, L K; TANG, P C; TSAI, J
PATENT ASSIGNEE(S): (CHEN-I) CHEN H; (GAZI-I) GAZIT A; (HIRT-I) HIRTH K P; (LEVI-I) LEVITZKI A; (MANN-I) MANN E; (SHAW-I) SHAWVER L K; (TANG-I) TANG P C; (TSAI-I) TSAI J; (SUGE-N) SUGEN INC; (YISS) YISSUM RES & DEV CO

COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2002068687	A1	20020606	(200317)*		58	C11D017-00<--
US 6596878	B2	20030722	(200356)			C07D231-38<--

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2002068687	A1	CIP of	US 1994-207933	19940307
		Cont of	US 1995-399967	19950307
		Cont of	US 1998-70318	19980429
		Cont of	US 2000-722149	20001122
			US 2001-953933	20010918
US 6596878	B2	CIP of	US 1994-207933	19940307
		Cont of	US 1995-399967	19950307
		Cont of	US 1995-486775	19950607
		Cont of	US 1998-70318	19980429
		Cont of	US 2000-722149	20001122
			US 2001-953933	20010918

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6596878	B2	Cont of	US 5773476
		Cont of	US 5789427

PRIORITY APPLN. INFO: US 1995-399967 19950307; US
1994-207933 19940307; US
1998-70318 19980429; US
2000-722149 20001122; US
2001-953933 20010918; US
1995-486775 19950607
INT. PATENT CLASSIF.:
MAIN: C07D231-38; C11D017-00
SECONDARY: C07C255-32; C07C255-33
BASIC ABSTRACT:
US2002068687 A UPAB: 20050112
NOVELTY - Protein kinase inhibitor composition comprises a thioamide compound (I).
DETAILED DESCRIPTION - Protein kinase inhibitor composition comprises a thioamide compound of formula (I).
R1-R3 = alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, NH2, NO2, thioether, SH, halo or H;
R5 = alkyl or a group of formula (i); and
X1-X5 = H, halo, alkyl, trihalomethyl or NO2.
INDEPENDENT CLAIMS are also included for:
(1) a HER-2 protein kinase inhibitor composition comprising a sulfone compound of formula (II);
(2) a protein kinase inhibitor composition comprising an amide compound of formula (III);
(3) a protein kinase inhibitor composition comprising a phenol compound of formula (IV);
(4) a protein kinase inhibitor composition comprising a compound of formula (V);
(5) a method of treating cell proliferative disorders by administering a compound of formula (VI);
(6) a method of treating a patient having cancer characterized by over-activity of HER-2 by administering a compound of formula (VII), (VIII) or (IX) or 2-bromomethyl-6,7-dimethyl-3-phenyl-quinoxaline, 1,3-bis((6,7-dimethyl-3-phenyl-quinoxalin-2-yl)-methylthio)propane, 2,6,7-trimethyl-3-phenyl-quinoxaline or 7,8-dimethyl-indeno(1,2-

b)quinoxalin-11-one;
(7) a method of treating a patient having cancer characterized by inappropriate activity of EGFR by administering a compound of formula (VI), (VII), (VIII), (IX) or 2-bromomethyl-6,7-dimethyl-3-phenyl-quinoxaline, 3-(3-bromo-4,5-dihydroxy-phenyl)-N-(3-(3-(3-bromo-4,5-dihydroxy-phenyl)-2-cyano-acryloylamino)-propyl)-2-cyano-acrylamide (AG-1075), 1,3-bis((6,7-dimethyl-3-phenyl-quinoxalin-2-yl)-methylthio)propane, 2,6,7-trimethyl-3-phenyl-quinoxaline, 6,7-dichloro-3-phenyl-quinoxaline or 7,8-dimethyl-indeno(1,2-b)quinoxalin-11-one; and
(8) a method of determining whether a receptor tyrosine kinase is important for growth of a cell by contacting the cell with a composition comprising a compound that inhibits growth of a receptor tyrosine kinase activity (EGF, PDGF or HER-2 activity), and measuring the growth of the cell.
R1a, R3a = alkyl, alkenyl, alkynyl, alkoxy or alkylaryl;
R4 = alkyl, alkylaryl, thioamide or amide;
R6-R10 = alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, NH2, NO2, thioether, SH, halo or H;
R12 = -C(=X6)X7;
X6 = O or S;
X7 = Me or trihalomethyl;
R13 = aryl or alkylaryl;
R4a = R4, CN or sulfonyl;
R12a = alkyl, alkenyl, alkynyl, alkoxy, ester, amide, thioamide, alkylaryl, trihalomethyl, CN, OH, NH2, NO2, thioether, SH or H;
R13a = aryl, alkyl, alkenyl, alkynyl, CN, alkylaryl, amide or thioamide;
R15-R19 = H, alkyl, alkenyl, alkynyl, alkoxy, OH, NO2, amine, thioether or SH;
R20 = alkyl, aryl or arylalkyl;
R21-R25 = H, halo, OH, SH, alkyl, aryl or trihaloalkyl;
R26 = CH2 or NH;
R27 = aryl or -C(CN)2;
R28 = absent or H; and
dotted line = optional double bond (when R28 is absent).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - Protein Tyrosine Kinase Inhibitor.
In cellular kinase inhibition assays, (3-Chloro-phenyl)-(6,7-dimethoxy-quinazolin-4-yl)-amine (AG-1478) inhibited EGFR (EGF-3T3) and HER-2 (BT474) with IC50 values of 0.003 and 1.4 micro M, respectively. In a growth assay, AG-1478 inhibited growth of A431 cells with an IC50 of 10 micro M.
USE - For treating cell proliferation disorders, especially cancer characterized by over-activity of HER-2, PDG or EGFR. Cancers include breast carcinomas, stomach adenocarcinomas, salivary gland adenocarcinomas, endometrial cancers, ovarian adenocarcinomas, gastric cancers, colorectal cancers and glioblastomas (claimed).
Dwg.0/7

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-D05; B06-D06; B10-A15; B10-A19; B10-B03; B10-B04; B14-D06; B14-H01

L4 ANSWER 3 OF 3 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-465990 [40] WPIX
CROSS REFERENCE: 1995-336717 [43]; 1998-387069 [33]; 2003-174010 [17]; 2005-030032 [03]
DOC. NO. CPI: C1998-141278
TITLE: New acrylonitrile derivatives are EFGR and HER2 inhibitors - useful for treatment of cell proliferation disorders e.g. cancer, glioblastoma, blood vessel proliferative disorders and fibrotic disorders.
DERWENT CLASS: B05
INVENTOR(S): CHEN, H; GAZIT, A; HIRTH, K P; MANN, E; SHAWVER, L K; TANG, P C; TSAI, J

PATENT ASSIGNEE(S): (SUGE-N) SUGEN INC; (YISS) YISSUM RES & DEV CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5789427	A	19980804	(199840)*		41	A01N043-40<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5789427	A CIP of	US 1994-207933	19940307
		US 1995-399967	19950307

PRIORITY APPLN. INFO: US 1995-399967 19950307; US 1994-207933 19940307
INT. PATENT CLASSIF.:
MAIN: A01N043-40
SECONDARY: C07D211-72
BASIC ABSTRACT:
US 5789427 A UPAB: 20050112
Acrylonitrile derivatives of formula (I) and their salts are new. R1-R3 = alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, OH, NH2, thioether, SH, halo, H, NO2 or amine; Y = C(CN)=CH, alkyl, NH-alkyl or is absent; R5 = CN or aryl; provided that if R5 = phenyl, R1-R3 are not alkoxy or OH and that at least one of R1-R3 is not H.

USE - (I) are used for the treatment of cell proliferation disorders, especially those characterised by inappropriate EGFR activity or over activity of HER2. Such disorders include breast carcinoma, stomach, salivary gland and ovarian adenocarcinomas, endometrial cancer, gastric cancer, colorectal cancer and glioblastoma (claimed). (I) are also useful for the treatment of blood vessel proliferative disorders and fibrotic disorders e.g. psoriasis and to diagnose activity of a particular receptor tyrosine kinase.

ADVANTAGE - (I) are selective for EFGR-kinase and HER2.

Dwg.0/7
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B10-A08; B10-A10; B14-F01; B14-H01; B14-H01B; B14-N17C

=> b home

FILE 'HOME' ENTERED AT 11:32:51 ON 08 JUN 2005

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L1            2 (US20040246684 OR US6596878 OR US20020068687 OR US5789427)/PN

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     FILE 'HCAPLUS' ENTERED AT 11:22:10 ON 08 JUN 2005
L2              TRA L1 1- RN :      133 TERMS

     FILE 'REGISTRY' ENTERED AT 11:22:11 ON 08 JUN 2005
L3          133 SEA L2

     FILE 'WPIX' ENTERED AT 11:22:14 ON 08 JUN 2005
L4            3 (US20040246684 OR US6596878 OR US20020068687 OR US5789427)/PN

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L6           49 L3 AND NR=2
L7              STR L5
L8            0 L7
L9            4 L7 FULL

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L10          19 L9

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L11           0 L9

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                E CHEN HUI/AU
L13        1276 E3-90
                E HIRTH K/AU
L14          36 E3-8
                E MANN E/AU
L15         110 E3-12,E19
                E SHAWVER L/AU
L16          63 E3-7
                E TSAI J/AU
L17         396 E3-27
                E TSAI JAINMING/AU
                E TSAI JIANMING/AU
L18           5 E3
                E TSAI JIAN/AU
L19           1 E5
                E TANG P/AU
L20          36 E3-4
                E TANG PENG CHO/AU
                E TANG PENG C/AU
L21          99 E3-4
L22         920 (SUGEN OR YISSUM)/CS,PA
L23           6 L10 AND L12-21
L24           8 L10 AND L22
L25           2 L24 NOT L23
L26          13 L10 NOT L23
L27          13 L26 OR L25

=> b reg
FILE 'REGISTRY' ENTERED AT 12:28:57 ON 08 JUN 2005
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STRUCTURE FILE UPDATES: 7 JUN 2005 HIGHEST RN 851848-50-5
DICTIONARY FILE UPDATES: 7 JUN 2005 HIGHEST RN 851848-50-5

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
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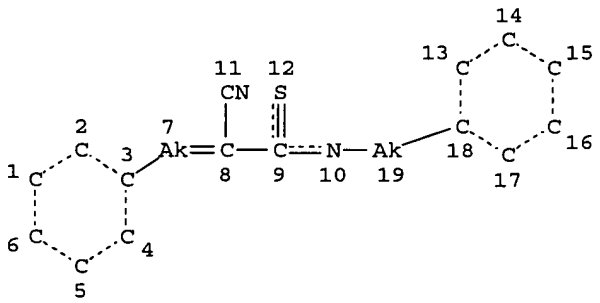
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que sta l9
L7 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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FILE COVERS 1907 - 8 Jun 2005 VOL 142 ISS 24
FILE LAST UPDATED: 7 Jun 2005 (20050607/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all fhitstr l23 tot

L23 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:718981 HCAPLUS
DN 131:322425
ED Entered STN: 11 Nov 1999
TI Preparation of phenylacrylonitriles, quinoxalines, quinazolines, and related compounds as modulators of tyrosine kinase signal transduction
IN App, Harald; McMahon, Gerald M.; **Tang, Peng Cho**; Gazit, Aviv; Levitzki, Alexander
PA Yissum Research Development Company of the Hebrew University of Jerusalem, Israel; Sugen, Inc.
SO U.S., 21 pp., Cont.-in-part of U.S. 5,712,395.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-275
ICS A61K031-40; A61K031-415; C07C317-28
INCL 514419000
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 28
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5981569	A	19991109	US 1995-463247	19950605
	CA 2149298	AA	19940526	CA 1993-2149298	19931115
	EP 1378570	A1	20040107	EP 2003-9148	19931115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 6177401	B1	20010123	US 1994-193829	19940209
	US 5712395	A	19980127	US 1995-386021	19950209
PRAI	US 1992-975750	B2	19921113		
	US 1993-38596	B2	19930326		
	US 1994-193829	A2	19940209		
	US 1995-386021	A2	19950209		
	EP 1994-900810	A3	19931115		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5981569	ICM	A61K031-275
	ICS	A61K031-40; A61K031-415; C07C317-28
	INCL	514419000
US 5981569	NCL	514/419.000; 514/407.000; 514/520.000; 514/521.000; 514/523.000; 514/525.000; 548/371.700; 548/494.000; 558/390.000; 558/393.000; 558/397.000; 558/401.000
	ECLA	A61K031/235; A61K031/275; A61K031/277; A61K031/38;

A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

EP 1378570 ECLA A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07K014/71; C07K016/28G; G01N033/50D2

US 6177401 NCL 514/001.000; 435/007.200; 436/501.000; 530/350.000; 530/399.000

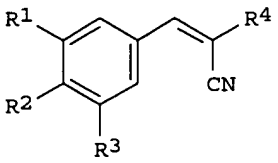
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

US 5712395 NCL 544/344.000; 544/353.000; 544/356.000

ECLA A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07D241/42; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/50D4

OS MARPAT 131:322425

GI



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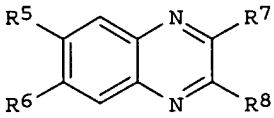

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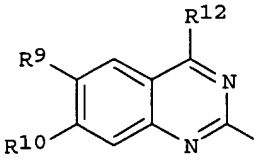

III

AB Title compds., e.g., [I, II, III; R1 = Me2CH, Me3C, iodo, Br, OH, Me; R2 = OH; R3 = Me2CH, Me3C, OH, H, Me; R4 = 1-phenyl-n-propylaminocarbonyl, (E)-1-cyano-2-[(3,5-diisopropyl-4-hydroxy)phenyl]ethenylsulfonyl, aminothiocarbonyl, cyanomethylsulfonyl, (3-amino-4-cyano)pyrazol-4-yl, etc.; R5, R6 = H, Me; R7 = H, CHO, Cl; R8 = Ph, 3,4-dihydroxyphenyl, 4-iodophenylamino, 3-chlorophenylamino, etc.; R9 = H, Me, OMe; R10 = H, OMe; R11 = H, Cl; R12 = 3-chlorophenylamino, 4-methylphenylmercapto, 4-iodophenylamino, 3-hydroxyphenylamino], were prepared as modulators of KDR/FLK-1 receptor signal transduction useful to regulate and/or modulate vasculogenesis and angiogenesis. Thus, 3,5-di-tert-butyl-4-hydroxybenzaldehyde, thiocyanoacetamide, and β-alanine were refluxed 6 h in EtOH to give (E)-2-aminothiocarbonyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)acrylonitrile. The latter showed IC50 = 0.8 μM in an in vitro FLK-1R ELISA assay.

ST phenylacrylonitrile quinoxaline quinazoline prepn tyrosine kinase signal transduction modulator; anticancer phenylacrylonitrile quinoxaline quinazoline; antidiabetic phenylacrylonitrile quinoxaline quinazoline; KDR FLK1 receptor signal transduction modulator phenylacrylonitrile

quinoxaline quinazoline; vasculogenesis modulator phenylacrylonitrile
quinoxaline quinazoline; angiogenesis modulator phenylacrylonitrile
quinoxaline quinazoline

IT Sarcoma
(Kaposi's, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Intestine, neoplasm
(colon, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Eye, disease
(diabetic retinopathy, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Neuroglia
(glioma, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Blood vessel, neoplasm
(hemangioma, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Angiogenesis
(modulators; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Prostate gland
(neoplasm, treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Antidiabetic agents
Antitumor agents
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Vascular endothelial growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT Lung, neoplasm
Melanoma
Ovary, neoplasm
Pancreas, neoplasm
Skin, neoplasm
(treatment; preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT 133550-18-2P 140674-76-6P 140674-77-7P 148741-30-4P 148741-31-5P
155566-32-8P 168835-80-1P 168835-82-3P 168835-83-4P 168835-85-6P
168835-87-8P 168835-88-9P 168835-89-0P 168835-90-3P
168835-91-4P 168835-92-5P 168835-93-6P 168835-94-7P 168835-95-8P
168835-96-9P 168835-97-0P 168835-98-1P 168836-00-8P 168836-01-9P
168836-02-0P 169120-56-3P 170448-92-7P 211370-16-0P 249296-58-0P
249296-59-1P 249296-66-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT 75-12-7, Formamide, reactions 95-76-1, 3,4-Dichloroaniline 99-40-1
100-46-9, Benzylamine, reactions 106-40-1, p-Bromoaniline 106-45-6,
p-Thiocresol 107-95-9, β-Alanine 108-42-9 109-77-3,
Malononitrile 123-08-0, 4-Hydroxybenzaldehyde 139-85-5,
3,4-Dihydroxybenzaldehyde 298-12-4, Glyoxylic acid 491-36-1,
4-Quinazolone 540-37-4, p-Iodoaniline 591-27-5 626-01-7,
3-Iodoaniline 771-97-1, 2,3-Diaminonaphthalene 1074-12-0,
Phenylglyoxal 1194-98-5, 2,5-Dihydroxybenzaldehyde 1196-69-6,
5-Formylindole 1620-98-0, 3,5-Di-tert-butyl-4-hydroxybenzaldehyde
1960-77-6 2078-54-8, 2,6-Diisopropylphenol 2740-81-0, 2-Chlorophenyl
isothiocyanate 2941-78-8, 5-Methyl-2-aminobenzoic acid 3171-45-7,
4,5-Dimethyl-1,2-diaminobenzene 3216-88-4 5438-36-8, 5-Iodovanillin
5653-40-7, 4,5-Dimethoxy-2-aminobenzoic acid 7357-70-2 10412-93-8,
N-Benzylcyanoacetamide 10537-86-7 16414-34-9, 5-Bromo-3,4-

dihydroxybenzaldehyde 28888-44-0, 6,7-Dimethoxy-2,4-quinazolinedione
37463-94-8 54711-21-6 58421-79-7, 4-Chloro-6-methylquinazoline
70071-08-8 93071-65-9, Methyl 3-aminomethylbenzoate 111233-69-3
133550-33-1 133550-57-9 168836-05-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

IT 5190-68-1P 13790-39-1P 13794-72-4P 19181-53-4P 27389-84-0P
27631-29-4P 28082-82-8P 29067-81-0P 168835-79-8P 170449-31-7P
170449-32-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

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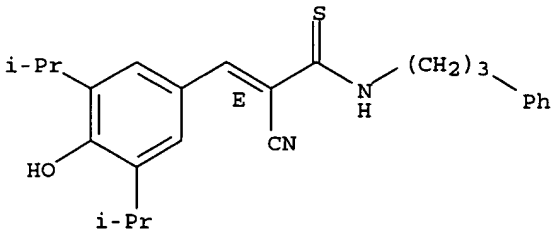
IT **168835-87-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of phenylacrylonitriles and related compds. as modulators of tyrosine kinase signal transduction)

RN 168835-87-8 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:545399 HCAPLUS
DN 129:175652
ED Entered STN: 27 Aug 1998
TI Preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction
IN App, Harald; Mcmahon, Gerald M.; **Tang, Peng Cho**; Gazit, Aviv; Levitzki, Alexander
PA Sugen, Inc., USA; Yissum Research Development Co. of the Hebrew University of Jerusalem
SO U.S., 20 pp., Cont.-in-part of U. S. 5,712,395.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-505
ICS A61K031-495; C07D239-93; C07D239-94
INCL 514259000
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5792771	A	19980811	US 1995-462391	19950605
	CA 2149298	AA	19940526	CA 1993-2149298	19931115
	EP 1378570	A1	20040107	EP 2003-9148	19931115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 6177401	B1	20010123	US 1994-193829	19940209
	US 5712395	A	19980127	US 1995-386021	19950209
PRAI	US 1992-975750	B2	19921113		
	US 1993-38596	B2	19930326		
	US 1994-193829	A2	19940209		
	US 1995-386021	A2	19950209		
	EP 1994-900810	A3	19931115		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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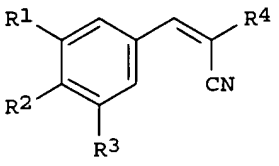
	ICS	A61K031-495; C07D239-93; C07D239-94
	INCL	514259000
US 5792771	NCL	514/266.300; 514/266.400; 544/250.000; 544/287.000; 544/293.000; 544/354.000; 544/356.000
	ECLA	A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V
EP 1378570	ECLA	A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07K014/71; C07K016/28G; G01N033/50D2

US 6177401 NCL 514/001.000; 435/007.200; 436/501.000; 530/350.000; 530/399.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

US 5712395 NCL 544/344.000; 544/353.000; 544/356.000
ECLA A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07D241/42; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/50D4

OS MARPAT 129:175652

GI



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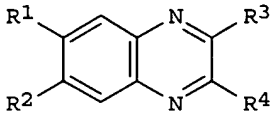

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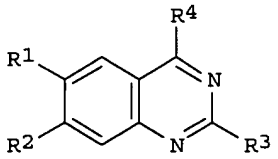

III

AB The title compds. [I, (R1 = iPr, tBu, I, etc.; R2 = OH; R3 = iPr, tBu, OH, etc.; R4 = (1-phenyl)-n-propylaminocarbonyl, cyanomethylsulfonyl, etc.), II (R1, R2 = Me, H; R1R2 = benzo; R3 = H, CHO, Cl; R4 = Ph, 3,4-(HO)2C6H4, (4-IC6H4)NH, etc.), III (R1 = MeO, Me, H; R2 = MeO; R3 = H, Cl; R4 = (3-ClC6H4)NH, (4-MeC6H4)S, (4-IC6H4)NH, etc.), etc.], capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction in order to regulate and/or modulate vasculogenesis and angiogenesis, were prepared Thus, reaction of 3,5-di-tert-butyl-4-hydroxybenzaldehyde with thiocyanoacetamide and β-alanine in EtOH afforded 54% (E)-I [R1, R3 = tBu; R2 = OH; R4 = C(S)NH2] which showed IC50 of 0.8 μM against protein tyrosine kinase at the FLK-1 receptor. The invention is based, in part, on the demonstration that KDR/FLK-1 tyrosine kinase receptor expression is associated with endothelial cells and the identification of vascular endothelial growth factor (VEGF) as the high affinity ligand of FLK-1. These results indicate a major role for KDR/FLK-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that express FLK-1 and the uses of expressed FLK-1 to evaluate and screen for drugs and analogs of VEGF involved in FLK-1 modulation by either agonist or antagonist activities is also described. The invention also relates to the use of the disclosed compds. in the treatment of disorders, including cancer, diabetes, diabetic retinopathy, rheumatoid arthritis, hemangioma and Kaposi's sarcoma, which are related to vasculogenesis and angiogenesis.

ST tyrosine kinase signal transduction quinazoline prepn; VEGF KDR tyrosine kinase quinazoline prepn; quinoxaline prepn tyrosine kinase signal

transduction; phenylacrylonitrile prepn tyrosine kinase signal transduction; antitumor agent quinoxaline quinazoline phenylacrylonitrile prepn; antidiabetic quinoxaline quinazoline phenylacrylonitrile prepn; hemangioma quinoxaline quinazoline phenylacrylonitrile prepn; Kaposi's sarcoma quinoxaline quinazoline phenylacrylonitrile prepn; rheumatoid arthritis quinoxaline quinazoline phenylacrylonitrile prepn; diabetic retinopathy quinoxaline quinazoline phenylacrylonitrile prepn; angiogenesis quinoxaline quinazoline phenylacrylonitrile prepn; vasculogenesis quinoxaline quinazoline phenylacrylonitrile prepn

IT Sarcoma
(Kaposi's, treatment of; preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT Eye, disease
(diabetic retinopathy, treatment of; preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT Blood vessel, neoplasm
(hemangioma, treatment of; preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT Angiogenesis
(modulation of; preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT Antidiabetic agents
Antitumor agents
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT Rheumatoid arthritis
(treatment of; preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT 150977-45-0, Flk-1/kdr vegf receptor tyrosine kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT 3458-44-4P 133550-18-2P 140674-76-6P 143993-61-7P 148741-30-4P
148741-31-5P 155566-32-8P 168835-80-1P 168835-81-2P 168835-82-3P
168835-83-4P 168835-84-5P 168835-85-6P **168835-87-8P**
168835-89-0P 168835-90-3P 168835-91-4P 168835-92-5P 168835-93-6P
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168836-00-8P 168836-01-9P 168836-02-0P 169120-56-3P 211370-16-0P
211370-17-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT 95-76-1, 3,4-Dichloroaniline 99-40-1 100-46-9, Benzylamine, reactions
106-40-1, p-Bromoaniline 106-45-6 108-42-9 109-77-3, Malononitrile
123-08-0, 4-Hydroxybenzaldehyde 139-85-5, 3,4-Dihydroxybenzaldehyde
298-12-4, Glyoxalic acid 491-36-1, 4(1H)-Quinazolinone 540-37-4,
p-Iodoaniline 591-27-5 619-45-4, Methyl 4-aminobenzoate 771-97-1,
2,3-Diaminonaphthalene 1074-12-0 1194-98-5, 2,5-Dihydroxybenzaldehyde
1196-69-6, 5-Formylindole 1620-98-0, 3,5-Di-tert-butyl-4-hydroxybenzaldehyde 1960-77-6 2078-54-8, 2,6-Diisopropylphenol
2740-81-0, 2-Chlorophenyl isothiocyanate 2941-78-8, 5-Methyl-2-aminobenzoic acid 3171-45-7, 4,5-Dimethyl-1,2-diaminobenzene 3216-88-4
5438-36-8, 5-Iodovanillin 5653-40-7, 4,5-Dimethoxy-2-aminobenzoic acid
7357-70-2, Cyanothioacetamide 16414-34-9, 5-Bromo-3,4-

dihydroxybenzaldehyde 28888-44-0, 6,7-Dimethoxy-2,4-quinazolinedione 37463-94-8 54711-21-6 70071-08-8 133550-33-1 133550-57-9 168836-05-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

IT 5190-68-1P 10537-86-7P 13790-39-1P 13794-72-4P 19181-53-4P 27389-84-0P 27631-29-4P 28082-82-8P 29067-81-0P, 2-Chloro-6,7-dimethylquinoxaline 58421-79-7P, 4-Chloro-6-methylquinazoline 168835-79-8P 170449-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

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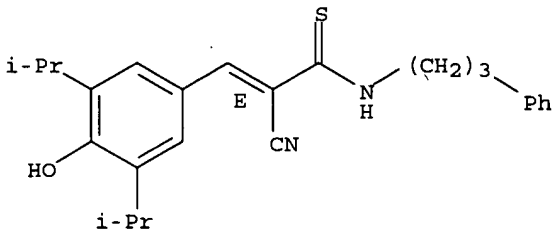
IT **168835-87-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines, quinoxalines and phenylacrylonitriles capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction)

RN 168835-87-8 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1998:534888 HCAPLUS

DN 129:156926

ED Entered STN: 24 Aug 1998

TI Methods and compositions using receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders, and inhibitor preparation

IN **Chen, Hui; Gazit, Aviv; Hirth, Klaus Peter; Mann, Elaina; Shawver, Laura K.; Tsai, Jianming;**

Tang, Peng Cho
PA Sugen, Inc., USA; Yissum Research & Development Company of the Hebrew University of Jerusalem
SO U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 207,933, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A01N043-40
ICS C07D211-72
INCL 514352000
CC 1-6 (Pharmacology)
Section cross-reference(s): 25, 28, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5789427	A	19980804	US 1995-399967	19950307
	US 5773476	A	19980630	US 1995-486775	19950607
	US 6596878	B2	20030722	US 2001-953933	20010918
	US 2004242684	A1	20041202	US 2003-602617	20030625
PRAI	US 1994-207933	B2	19940307		
	US 1995-399967	A1	19950307		
	US 1995-486775	A1	19950607		
	US 1998-70318	B1	19980429		
	US 2000-722149	B1	20001122		
	US 2001-953933	A3	20010918		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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	ICS	C07D211-72
	INCL	514352000
US 5789427	NCL	514/352.000; 514/357.000; 546/304.000; 546/330.000
	ECLA	A61K031/245+A; A61K031/277; A61K031/415+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C255/66; C07C311/27; C07C317/46; C07C327/44; C07D241/52B1; C07D241/52B5
US 5773476	NCL	514/620.000; 514/618.000; 514/619.000; 564/162.000; 564/164.000; 564/165.000; 564/167.000; 564/168.000; 564/170.000
	ECLA	C07C229/60; C07C255/41; C07C255/66
US 6596878	NCL	548/371.700; 558/402.000; 558/404.000
	ECLA	A61K031/245+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C255/66; C07C311/27; C07C317/46; C07C327/44; C07D241/52B1; C07D241/52B5; A61K031/277; A61K031/415+A
US 2004242684	NCL	514/521.000; 558/401.000
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OS MARPAT 129:156926
AB The invention concerns compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders, e.g. cancers characterized by over-activity or inappropriate activity HER2 or EGFR.
ST receptor tyrosine kinase inhibitor prepn antiproliferative; antitumor receptor tyrosine kinase inhibitor prepn; HER2 EGFR kinase inhibitor antiproliferative antitumor
IT Animal cell line
(A431; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)
IT Ovary, neoplasm
Salivary gland

Salivary gland
Salivary gland
Stomach, neoplasm
Stomach, neoplasm
(adenocarcinoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Mammary gland
(carcinoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(chimeric, EGFR-HER2; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Intestine, neoplasm
Intestine, neoplasm
(colorectal, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Antitumor agents
(colorectal; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Uterus, neoplasm
Uterus, neoplasm
(endometrium, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Antitumor agents
(endometrium; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Antitumor agents
(gastric adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Neuroglia
(glioblastoma, inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(glioblastoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Ovary, neoplasm
Stomach, neoplasm
(inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(mammary gland carcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(ovary adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(ovary; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Proliferation inhibition
(proliferation inhibitors; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
Cytotoxic agents
Drug delivery systems
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Epidermal growth factor receptors
Growth factor receptors
neu (receptor)
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Platelet-derived growth factor receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(salivary gland adenocarcinoma; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT Antitumor agents
(stomach; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 1960-77-6P 5190-68-1P, 4-Chloroquinazoline 10537-86-7P, 3,5-Diisopropyl-4-hydroxybenzaldehyde 19181-54-5P 27389-84-0P 29634-62-6P 170449-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 93-91-4, Benzoyl acetone 94-02-0, Ethyl benzoyl acetate 98-16-8 99-40-1 100-46-9, Benzylamine, reactions 103-79-7, Phenyl acetone 105-34-0, Methyl cyanoacetate 108-42-9, 3-Chloroaniline 109-76-2, 1,3-Propanediamine 109-77-3, Malononitrile 109-80-8, 1,3-Propanedithiol 120-46-7, Dibenzoyl methane 123-54-6, 2,4-Pentanedione, reactions 139-85-5, 3,4-Dihydroxybenzaldehyde 480-96-6, Benzofuroxane 485-47-2, Ninhydrin 491-36-1, 4-Quinazolinone 579-07-7 868-54-2, Malononitrile dimer 1075-06-5, Phenyl glyoxal hydrate 1194-98-5, 2,5-Dihydroxybenzaldehyde 1620-98-0, 3,5-Di-tert-butyl-4-hydroxybenzaldehyde 2038-57-5, 3-Phenylpropylamine 2078-54-8, 2,6-Diisopropylphenol 2423-66-7 2941-78-8, 5-Methyl-2-aminobenzoic acid 3171-45-7 4389-45-1, 2-Amino-3-methylbenzoic acid 4518-10-9 5348-42-5, 4,5-Dichloro-1,2-phenylenediamine 5438-36-8, 5-Iodovanillin 7357-70-2 10412-93-8, N-Benzylcyanoacetamide 13790-39-1, 4-Chloro-6,7-dimethoxyquinazoline 14268-66-7, 3,4-Methylenedioxyaniline 16414-34-9, 3,4-Dihydroxy-5-bromobenzaldehyde 24522-30-3 27869-04-1 37463-94-8 40018-25-5, 2-Chlorobenzoylacetonitrile 54711-21-6 58421-79-7, 4-Chloro-6-methylquinazoline 74908-81-9 133550-33-1 138942-61-7 168835-79-8 170449-33-9 170449-34-0, 2-Pyridinesulfonylacetonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 79079-06-4, EGF receptor tyrosine kinase 127407-08-3, Receptor tyrosine kinase 137632-09-8, HER2 kinase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 101463-26-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 13494-38-7P 65224-45-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 555-60-2P 5023-53-0P 5784-78-1P 6639-86-7P 10537-47-0P
13297-17-1P 15034-21-6P 23190-84-3P 40114-83-8P 54259-09-5P
57859-60-6P 70071-08-8P 71896-95-2P 88404-44-8P 140674-76-6P
146871-70-7P 148741-30-4P 148741-31-5P **148741-32-6P**
153436-53-4P 168835-82-3P **168835-87-8P** 170448-89-2P
170448-90-5P 170448-91-6P 170448-92-7P 170449-00-0P 170449-12-4P
170449-13-5P 170449-14-6P 170449-15-7P 170449-16-8P 170449-17-9P
170449-18-0P 170449-19-1P 170449-20-4P 170449-21-5P 170449-22-6P
170449-23-7P 170449-24-8P 170449-25-9P 211298-73-6P 211298-75-8P
211298-81-6P 211298-83-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 65678-07-1 133550-41-1 170448-88-1 170448-95-0 170448-97-2
170448-98-3 170448-99-4 170449-02-2 170449-03-3 170449-04-4
170449-05-5 170449-06-6 170449-07-7 170449-08-8 170449-11-3
170449-26-0 170449-27-1 170449-28-2 170449-29-3 170449-30-6
186581-94-2 186581-95-3 186581-96-4 211299-44-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

IT 15762-68-2P 19181-53-4P, 6-Methyl-4-quinazolinone 58421-80-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

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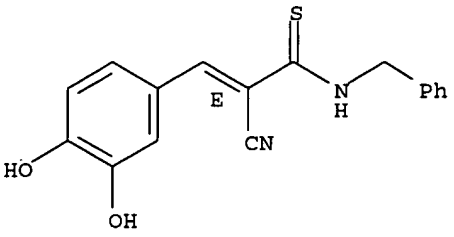
IT **148741-32-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors, and preparation thereof, for inhibiting cell proliferative disorders)

RN 148741-32-6 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-,

(2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



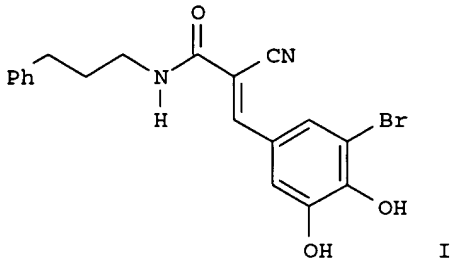
L23 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:405435 HCAPLUS
DN 129:54393
ED Entered STN: 02 Jul 1998
TI Preparation of compounds for the treatment of disorders related to vasculogenesis and/or angiogenesis
IN App, Harald; McMahon, Gerald M.; **Tang, Peng Cho**; Gazit, Aviv; Levitzki, Alexander
PA Sugen, Inc., USA; Yissum Research Development
SO U.S., 19 pp., Cont.-in-part of U.S. 5,712,395.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D241-40
ICS C07D241-42; A61K031-495; A61K031-50
INCL 514249000
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5763441	A	19980609	US 1995-462046	19950605
	CA 2149298	AA	19940526	CA 1993-2149298	19931115
	EP 1378570	A1	20040107	EP 2003-9148	19931115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 6177401	B1	20010123	US 1994-193829	19940209
	US 5712395	A	19980127	US 1995-386021	19950209
PRAI	US 1992-975750	B2	19921113		
	US 1993-38596	B2	19930326		
	US 1994-193829	A2	19940209		
	US 1995-386021	A2	19950209		
	EP 1994-900810	A3	19931115		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5763441	ICM	C07D241-40
	ICS	C07D241-42; A61K031-495; A61K031-50
	INCL	514249000
US 5763441	NCL	514/249.000; 514/250.000
	ECLA	A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V
EP 1378570	ECLA	A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07K014/71; C07K016/28G; G01N033/50D2

US 6177401 NCL 514/001.000; 435/007.200; 436/501.000; 530/350.000; 530/399.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V
US 5712395 NCL 544/344.000; 544/353.000; 544/356.000
ECLA A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07D241/42; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/50D4
OS MARPAT 129:54393
GI



I

AB Title compds., e.g., (E)-HOZCH:CR4CN (R4 = CONHR, SO2CH2CN, etc.; R = aralkyl, etc.; Z = 2-substituted-1,4-phenylene, 2,6-disubstituted-1,4-phenylene), capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction in order to regulate and/or modulate vasculogenesis and angiogenesis, were prepared Thus, 5-iodovanillin was condensed with Ph(CH2)3NHCOCH2CN to give, after O-demethylation, title compound I. Data for biol. activity of title compds. were given.

ST angiogenesis disorder treatment compd prepn; KDR FLK1 receptor modulator prepn

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(gene KDR; preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT Angiogenesis inhibitors
Antitumor agents
(preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 3458-44-4P 133550-18-2P 140674-76-6P 143993-61-7P 148741-30-4P 148741-31-5P 168835-80-1P 168835-81-2P 168835-82-3P 168835-83-4P 168835-84-5P 168835-85-6P **168835-87-8P** 168835-88-9P 168835-89-0P 168835-90-3P 168835-93-6P 168835-95-8P 168835-96-9P 168835-98-1P, 2-PhenylBenzo[g]quinoxaline 168836-00-8P 168836-01-9P 168836-02-0P 168836-03-1P 168836-04-2P 169120-56-3P 183322-24-9P 202525-93-7P 208707-95-3P 208707-96-4P 208707-97-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 95-76-1, 3,4-Dichloroaniline 99-40-1, 2-Chloro-1-(3,4-dihydroxyphenyl)ethanone 100-46-9, Benzylamine, reactions 106-40-1,

p-Bromoaniline 106-45-6, p-Thiocresol 108-42-9 109-77-3, Malononitrile 123-08-0, 4-Hydroxybenzaldehyde 139-85-5, 3,4-Dihydroxybenzaldehyde 491-36-1, 4-Quinazolone 540-37-4, p-Iodoaniline 771-97-1, 2,3-Diaminonaphthalene 1118-60-1, Diacetonitrile 1194-98-5, 2,5-Dihydroxybenzaldehyde 1196-69-6, 5-Formylindole 1620-98-0, 3,5-Di-tert-butyl-4-hydroxybenzaldehyde 1960-77-6, Acetamide, 2-cyano-N-(3-trifluoromethylphenyl)- 2078-54-8, 2,6-Diisopropylphenol 2740-81-0, 2-Chlorophenyl isothiocyanate 2941-78-8, 2-Amino-5-methylbenzoic acid 3171-45-7, 1,2-Diamino-4,5-dimethylbenzene 5438-36-8, 5-Iodovanillin 10412-93-8, N-Benzylcyanoacetamide 28888-44-0, 6,7-Dimethoxy-2,4-quinazolinedione 37463-94-8, Sulfonyldiacetonitrile 54711-21-6 133550-33-1, Acetamide, 2-cyano-N-(3-Phenylpropyl)- 133550-57-9, 2-Cyano-1-(3,4-dihydroxyphenyl)ethanone 168836-05-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 5190-68-1P, 4-Chloroquinazoline 10537-86-7P, 3,5-Diisopropyl-4-hydroxybenzaldehyde 19181-53-4P, 6-Methyl-4-quinazolone 27389-84-0P 27631-29-4P, 2,4-Dichloro-6,7-Dimethoxyquinazoline 28082-82-8P 29067-81-0P 58421-79-7P, 4-Chloro-6-Methylquinazoline 168835-79-8P 170449-31-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

RE.CNT 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD

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(10) Anon; WO 9203459 1992 HCAPLUS
(11) Anon; WO 9214748 1992 HCAPLUS
(12) Anon; WO 9217486 1992 HCAPLUS
(13) Anon; WO 9220642 1992 HCAPLUS
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(15) Anon; WO 9403427 1994 HCAPLUS
(16) Anon; WO 9410202 1994 HCAPLUS
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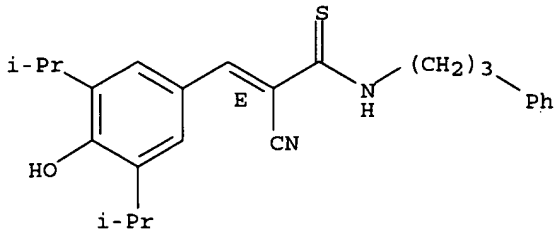
IT **168835-87-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

RN 168835-87-8 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:115367 HCAPLUS
DN 128:154102
ED Entered STN: 26 Feb 1998
TI Quinazolines, quinoxalines, acrylonitriles, and other compounds for the treatment of disorders related to vasculogenesis and/or angiogenesis
IN App, Harald; McMahon, Gerald M.; **Tang, Peng Cho**; Gazit, Aviv; Levitzki, Alexander
PA Yissum Research Development Corp., Israel; Sugen
SO U.S., 16 pp., Cont.-in-part of U.S. Ser. No. 193,829, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D241-38
INCL 544344000
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 25
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5712395	A	19980127	US 1995-386021	19950209
	CA 2149298	AA	19940526	CA 1993-2149298	19931115
	EP 1378570	A1	20040107	EP 2003-9148	19931115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	US 6177401	B1	20010123	US 1994-193829	19940209
	US 5763441	A	19980609	US 1995-462046	19950605
	US 5792771	A	19980811	US 1995-462391	19950605
	US 5981569	A	19991109	US 1995-463247	19950605
	US 5849742	A	19981215	US 1997-853239	19970509
PRAI	US 1992-975750	B2	19921113		
	US 1993-38596	B2	19930326		
	US 1994-193829	B2	19940209		
	EP 1994-900810	A3	19931115		
	US 1995-386021	A2	19950209		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5712395	ICM	C07D241-38
	INCL	544344000
US 5712395	NCL	544/344.000; 544/353.000; 544/356.000
	ECLA	A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07D241/42; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/50D4
EP 1378570	ECLA	A61K031/277; A61K031/502; A61K031/517; C07D209/18; C07K014/71; C07K016/28G; G01N033/50D2
US 6177401	NCL	514/001.000; 435/007.200; 436/501.000; 530/350.000; 530/399.000
	ECLA	A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44;

C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

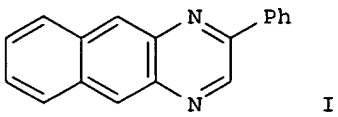
US 5763441 NCL 514/249.000; 514/250.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

US 5792771 NCL 514/266.300; 514/266.400; 544/250.000; 544/287.000; 544/293.000; 544/354.000; 544/356.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

US 5981569 NCL 514/419.000; 514/407.000; 514/520.000; 514/521.000; 514/523.000; 514/525.000; 548/371.700; 548/494.000; 558/390.000; 558/393.000; 558/397.000; 558/401.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

US 5849742 NCL 514/249.000; 514/250.000; 544/344.000; 544/353.000; 544/356.000
ECLA A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D231/38B3A; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71; C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

OS MARPAT 128:154102
GI



I

AB The invention relates to a wide variety of organic mols. capable of modulating tyrosine kinase signal transduction, and particularly KDR/FLK-1 receptor signal transduction, in order to regulate and/or modulate vasculogenesis and angiogenesis. The invention is based, in part, on the demonstration that KDR/FLK-1 tyrosine kinase receptor expression is associated with endothelial cells, and the identification of vascular endothelial growth factor (VEGF) as the high-affinity ligand of FLK-1. These results indicate a major role for KDR/FLK-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that

express FLK-1 and the uses of expressed FLK-1 to evaluate and screen for drugs and analogs of VEGF involved in FLK-1 modulation by either agonist or antagonist activities is also described. The invention also relates to the use of the disclosed compds. in the treatment of disorders, including cancer, diabetes, hemangioma and Kaposi's sarcoma, which are related to vasculogenesis and angiogenesis. Examples include prepns. of about 30 title compds., and a variety of bioassays. For instance, cyclocondensation of 2,3-diaminonaphthalene with phenylglyoxal in refluxing EtOH gave 65% of the claimed title compound 2-phenyl-1,4-diazaanthracene (I). The latter compound gave 41% inhibition of growth of Calu-6 human lung cancer xenografts in immunocompetent mice when given at a rate of 20 mg/kg/day.

ST angiogenesis inhibitor quinoxaline quinazoline acrylonitrile prepn; vasculogenesis inhibitor quinoxaline quinazoline nitrile prepn

IT Vascular endothelial growth factor receptors
Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene KDR; preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT Angiogenesis inhibitors
Antitumor agents
Blood vessel
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 75706-12-6, Leflunomide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 3458-44-4P 133550-18-2P 140674-76-6P 143993-61-7P 148741-30-4P
148741-31-5P 155566-32-8P 168835-80-1P 168835-81-2P 168835-82-3P
168835-83-4P 168835-84-5P 168835-85-6P 168835-86-7P
168835-87-8P 168835-88-9P 168835-89-0P 168835-90-3P
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168835-96-9P 168835-97-0P 168835-98-1P 168835-99-2P 168836-00-8P
168836-01-9P 168836-02-0P 168836-03-1P 168836-04-2P 183322-24-9P
202525-93-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 127464-60-2, Vascular endothelial growth factor 150977-45-0, Flk-1/KDR VEGF receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 95-76-1, 3,4-Dichloroaniline 99-40-1 100-46-9, Benzylamine, reactions 106-40-1, p-Bromoaniline 106-45-6, Benzenethiol, 4-methyl- 107-95-9, β-Alanine 108-42-9 109-77-3, Malononitrile 123-08-0 139-85-5, 3,4-Dihydroxybenzaldehyde 298-12-4, Glyoxalic acid 491-36-1, 4(1H)-Quinazolinone 540-37-4, p-Iodoaniline 591-27-5 626-01-7, 3-Iodoaniline 771-97-1, 2,3-Naphthalenediamine 1074-12-0, Phenylglyoxal 1196-69-6, 5-Formylindole 1620-98-0 1960-77-6, Acetamide, 2-cyano-N-[3-(trifluoromethyl)phenyl]- 2078-54-8, 2,6-Diisopropylphenol 2740-81-0, 2-Chlorophenyl isothiocyanate 2941-78-8, 2-Amino-5-methylbenzoic acid 3171-45-7, 4,5-Dimethyl-1,2-benzenediamine 3216-88-4 5438-36-8, 5-Iodovanillin 5653-40-7, 2-Amino-4,5-dimethoxybenzoic acid 5875-28-5, Thiocyanatoacetamide 10412-93-8, N-Benzylcyanoacetamide 16414-34-9, 5-Bromo-3,4-dihydroxybenzaldehyde 28888-44-0, 6,7-Dimethoxy-2,4-quinazolinedione 37463-94-8, Sulfonyldiacetonitrile 133550-33-1, Acetamide, 2-cyano-N-(3-phenylpropyl)- 133550-57-9 168836-05-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 5190-68-1P, 4-Chloroquinazoline 10537-86-7P, 3,5-Diisopropyl-4-hydroxybenzaldehyde 13790-39-1P, 4-Chloro-6,7-dimethoxyquinazoline 13794-72-4P, 4(3H)-Quinazolinone, 6,7-dimethoxy 19181-53-4P, 4(1H)-Quinazolinone, 6-methyl- 27389-84-0P 27631-29-4P, 2,4-Dichloro-6,7-dimethoxyquinazoline 28082-82-8P, 2(1H)-Quinoxalinone, 6,7-dimethyl- 29067-81-0P, Quinoxaline, 2-chloro-6,7-dimethyl- 54711-21-6P 58421-79-7P, 4-Chloro-6-methylquinazoline 70071-08-8P 168835-78-7P 168835-79-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

IT 80449-02-1, Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signal transduction; preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; DE 1135471 1962 HCAPLUS
(2) Anon; JP 55-167205 1980 HCAPLUS
(3) Anon; EP 520722 1992 HCAPLUS
(4) Baumann; US 4001017 1977 HCAPLUS
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(11) Ohmichi, M; Biochemistry 1993, V32, P4650 HCAPLUS
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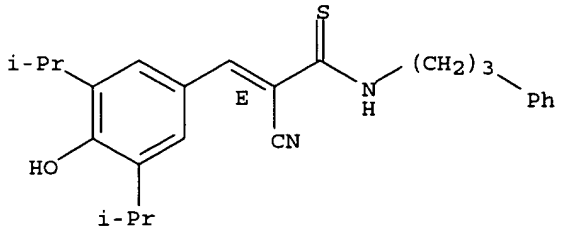
(15) Soper; US 3647793 1972 HCAPLUS
(16) Spada; US 5480883 1996 HCAPLUS
(17) Stout, D; J Med Chem 1983, V26, P808 HCAPLUS
(18) Vogel, M; Journal f prakt Chemie 1987, P101 HCAPLUS

IT **168835-87-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines, quinoxalines, acrylonitriles, and other compds. as vasculogenesis and/or angiogenesis inhibitors)

RN 168835-87-8 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:926425 HCAPLUS

DN 123:329984

ED Entered STN: 17 Nov 1995

TI Receptor tyrosine kinase inhibitors for inhibiting cell proliferative

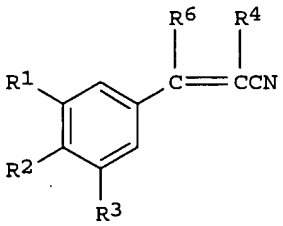
disorders
IN **Chen, Hui**; Gazit, Aviv; **Hirth, Klaus Peter**; Levitzki, Alex; **Mann, Elaina**; **Shawver, Laura K.**; **Tsai, Jianming**; **Tang, Peng Cho**
PA Sugen, Inc., USA; Yissum Research Development Co.
SO PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-275
ICS A61K031-495; C07C327-44; C07C311-13; C07C317-14; C07C255-34; C07D241-52
CC 1-6 (Pharmacology)
Section cross-reference(s): 7, 25
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9524190	A2	19950914	WO 1995-US2826	19950306
WO 9524190	A3	19951109		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9520968	A1	19950925	AU 1995-20968	19950306
PRAI US 1994-207933	A	19940307		
WO 1995-US2826	W	19950306		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9524190	ICM	A61K031-275
	ICS	A61K031-495; C07C327-44; C07C311-13; C07C317-14; C07C255-34; C07D241-52
WO 9524190	ECLA	A61K031/245+A; A61K031/277; A61K031/415+A; A61K031/4184; A61K031/4402; A61K031/498; A61K031/517; C07C229/60; C07C255/36; C07C255/37; C07C255/41; C07C255/42; C07C311/27; C07C317/46; C07C327/44; C07D241/52B5; C07D241/52B1

OS MARPAT 123:329984
GI



I

AB Receptor tyrosine kinase inhibitors I [R1-R3, R6 = alkyl, alkenyl, alkynyl, alkoxy, OH, amino, SH, alkylthio, halo, H, NO2, etc.; R4 = C(S)NHR5, C(O)NHR5, SO2YR5; Y = single bond, C(CN):CH:CH, azaalkyl; R5 = (substituted) aralkyl, CN] and II [R7-R10 = R1-R3 above; R12 = C(O)Me, C(S)Me, C(O)CF3, C(S)CF3; R13 = aryl, alkylaryl] are prepared for use in treating cell proliferative disorders such as cancers characterized by overactivity or inappropriate activity of HER2 receptors or EGF receptors. Thus, I [R1, R2 = OH, R3 = I, R4 = C(O)NH(CH2)3Ph, R6 = H] (III) was prepared in 2 steps by condensation of 5-iodovanillin with N-(3-phenylpropyl)cyanoacetamide. III inhibited EGF receptor kinase

activity in EGC7 cells, HER2 kinase activity in BT-474 cells, and platelet-derived growth factor receptor kinase β activity with an IC50 of 4, 18, and 35 μM, resp., and inhibited growth of SKBR3 and SKOV3 cells in vitro at IC50 9 and 4.5 μM, resp.

ST receptor tyrosine kinase inhibitor prepn cancer; protein tyrosine kinase inhibitor cell proliferation

IT Neoplasm inhibitors
Stomach, neoplasm
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Ovary, neoplasm
Stomach, neoplasm
(adenocarcinoma, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Animal growth regulator receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood platelet-derived growth factor, overactivity of, neoplasm from; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Uterus, neoplasm
(endometrium, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(epidermal growth factor/α-transforming growth factor, gene c-erbB, receptor, protein tyrosine kinase of, inhibitors of; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Intestine, neoplasm
(large, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Mammary gland
(neoplasm, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Salivary gland
(neoplasm, adenocarcinoma, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Mammary gland
(neoplasm, carcinoma, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Neuroglia
(neoplasm, glioblastoma, receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p185c-erbB2, inhibitors; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT Animal growth regulator receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α-transforming growth factor gene c-erbB, receptor, protein tyrosine kinase of, inhibitors of; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT 80449-02-1, Protein tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT 101463-26-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(protein tyrosine kinase of, inhibitors of; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT 555-60-2P 5023-53-0P 5784-78-1P 6639-86-7P 10537-47-0P
13297-17-1P 13494-38-7P 15034-21-6P 23190-84-3P 40114-83-8P
54259-09-5P 57859-60-6P 65224-45-5P 65678-07-1P 70071-08-8P
71896-95-2P 88404-44-8P 133550-41-1P 140674-76-6P 146871-70-7P
148741-30-4P 148741-31-5P **148741-32-6P** 153436-53-4P
168835-81-2P 168835-82-3P 168835-83-4P **168835-87-8P**

170448-88-1P 170448-89-2P 170448-90-5P 170448-91-6P 170448-92-7P
170448-94-9P 170448-95-0P 170448-96-1P 170448-97-2P 170448-98-3P
170448-99-4P 170449-00-0P 170449-01-1P 170449-02-2P 170449-03-3P
170449-04-4P 170449-05-5P 170449-06-6P 170449-07-7P 170449-08-8P
170449-09-9P 170449-10-2P 170449-11-3P 170449-12-4P 170449-13-5P
170449-14-6P 170449-15-7P 170449-16-8P 170449-17-9P 170449-18-0P
170449-19-1P 170449-20-4P 170449-21-5P 170449-22-6P 170449-23-7P
170449-24-8P 170449-25-9P 170449-26-0P 170449-27-1P 170449-28-2P
170449-29-3P 170449-30-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT 93-91-4, Benzoylacetone 94-02-0, Ethyl benzoylacetate 98-16-8, 3-Trifluoromethylaniline 99-40-1 100-46-9, Benzylamine, reactions 103-79-7, Phenylacetone 105-34-0, Methyl cyanoacetate 108-42-9, 3-Chloroaniline 109-76-2, 1,3-Propanediamine 109-77-3, Malononitrile 109-80-8, 1,3-Propanedithiol 120-46-7, Dibenzoylmethane 123-54-6, Acetylacetone, reactions 139-85-5, 3,4-Dihydroxybenzaldehyde 480-96-6, Benzofuroxane 485-47-2, Ninhydrin 491-36-1, 4-Quinazolinone 579-07-7 619-45-4, Methyl 4-aminobenzoate 704-13-2, 3-Hydroxy-4-nitrobenzaldehyde 868-54-2, Malononitrile dimer 1074-12-0, Phenylglyoxal 1194-98-5, 2,5-Dihydroxybenzaldehyde 1620-98-0 2038-57-5, 3-Phenylpropylamine 2078-54-8, 2,6-Diisopropylphenol 2233-18-3, 3,5-Dimethyl-4-hydroxybenzaldehyde 2941-78-8, 5-Methyl-2-aminobenzoic acid 3171-45-7, 4,5-Dimethyl-1,2-phenylenediamine 4389-45-1, 2-Amino-3-methylbenzoic acid 5348-42-5, 4,5-Dichloro-1,2-phenylenediamine 5438-36-8, 5-Iodovanillin 7357-70-2 7605-28-9, Phenylsulfonylacetonitrile 10412-93-8, N-Benzylcyanoacetamide 13790-39-1, 4-Chloro-6,7-dimethoxyquinazoline 14268-66-7, 3,4-Methylenedioxyaniline 16414-34-9 24522-30-3 27869-04-1 37463-94-8, Sulfonyldiacetonitrile 40018-25-5 54711-21-6 58421-79-7, 4-Chloro-6-methylquinazoline 105640-66-2 133550-33-1 168835-79-8 170449-34-0 170449-35-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

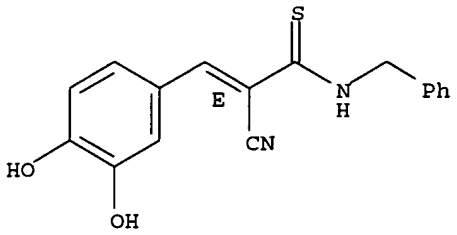
IT 1960-77-6P 5190-68-1P, 4-Chloroquinazoline 10537-86-7P 19181-53-4P 19181-54-5P 27389-84-0P 29634-62-6P 58421-80-0P 111233-69-3P 170449-31-7P 170449-32-8P 170449-33-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT 62229-50-9, EGF 79079-06-4, EGF receptor protein tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptor, protein tyrosine kinase of, inhibitors of; receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

IT **148741-32-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

RN 148741-32-6 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



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L27 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:253721 HCAPLUS
DN 141:307821
ED Entered STN: 29 Mar 2004
TI Pro-apoptotic and anti-apoptotic molecules affecting pathways of signal transduction
AU Keri, G.; Racz, G.; Magyar, K.; Oerfi, L.; Horvath, A.; Schwab, R.; Hegymegi, B. B.; Szende, B.
CS Research Group of Peptide Biochemistry of Hungarian Academy of Sciences in the Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, H-1088, Hung.
SO Annals of the New York Academy of Sciences (2003), 1010(Apoptosis), 109-112
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
CC 2-5 (Mammalian Hormones)
Section cross-reference(s): 1
AB Selective inhibition of the "false" proliferative signals via targeting tyrosine kinases resulting in the induction of apoptosis by depletion of the "survival factors" is one of the most studied and widely accepted concepts of modern chemotherapy. We have synthesized a series of potent tyrosine kinase inhibitors and tested these compds. for apoptosis induction. Some of the tyrosine kinase inhibitors caused either apoptotic or cytoplasmic vacuolar cell death in various tumor cell cultures. The somatostatin analog oligopeptide TT-232, which indirectly inhibits tyrosine kinases, exerted a dose-dependent apoptosis-inducing effect. The tumor growth-inhibitory effect of TT-232 and some tyrosine kinase inhibitors has also been proven by in vivo expts., using human tumor xenografts. On the other hand, a dose-dependent pro- or anti-apoptotic activity of (-)-deprenyl has been shown in melanoma cell cultures, the lower doses inhibiting and the higher doses inducing apoptosis. Various metabolites of (-)-deprenyl are responsible for these actions. The effect of (-)-deprenyl is connected with depolarization of mitochondrial membranes. The kinase inhibitors act on the growth factor receptor signaling pathways (survival factor pathways) and initiate the caspase cascade. The key enzyme for the action of both pro-apoptotic and anti-apoptotic compds. is caspase 3.
ST apoptosis mol signal transduction tyrosine kinase inhibitor antitumor tumor
IT Epidermal growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(EGF receptor-specific tyrphostin AG-213 dose-dependently decreased number of cultured HT-29 cells and showed retardation of growth of HT-29 tumor xenograft in mouse)
IT Intestine, neoplasm
(colon, carcinoma; tyrphostin AG-213 dose-dependently decreased number of cultured HT-29 cells and showed retardation of growth of HT-29 tumor

xenograft in mouse)
IT Carcinoma
(colon; tyrphostin AG-213 dose-dependently decreased number of cultured HT-29 cells and showed retardation of growth of HT-29 tumor xenograft in mouse)
IT Signal transduction, biological
(kinase inhibitors act on growth factor receptor signaling pathways (survival factor pathways) and initiate caspase cascade in HT-29 cell culture and in mouse bearing HT-29 human colon carcinoma cells in vivo)
IT Neoplasm
(somatostatin analog oligopeptide TT-232 administration significantly decreased tumor mass, mitotic index and increased apoptotic index in mouse bearing HT-29 colon carcinoma cells)
IT Human
(somatostatin analog oligopeptide TT-232 administration which indirectly inhibits tyrosine kinases exerted dose-dependent apoptosis-inducing effect in HT-29 cell culture)
IT Apoptosis
Drug targets
(somatostatin analog oligopeptide TT-232 administration which indirectly inhibits tyrosine kinases exerted dose-dependent apoptosis-inducing effect on in vitro HT-29 cell culture and reduced tumor mass in mouse xenograft)
IT 14611-51-9, (-)-Deprenyl
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((-)-deprenyl administration showed dose-dependent pro- and anti-apoptotic activity, lower doses inhibited and higher dose induced apoptosis in M-1 melanoma cells)
IT 169592-56-7, Caspase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
((-)-deprenyl increased caspase 3 activity and showed no activity at lower doses in M-1 melanoma cell)
IT 71308-35-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG 17; tyrosine kinase inhibitor AG17 showed less apoptosis-inducing effect in HT-29 cell culture)
IT 9001-66-5, Monoamine oxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MAO-B inhibitor (-)-deprenyl administration showed dose-dependent pro- and anti-apoptotic activity, lower doses inhibited and higher doses induced apoptosis in M-1 melanoma cells)
IT 147159-51-1, TT-232
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(somatostatin analog oligopeptide TT-232 administration which indirectly inhibits tyrosine kinases exerted dose-dependent apoptosis-inducing effect in HT-29 cell culture)
IT 80449-02-1, Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(somatostatin analog oligopeptide TT-232 administration which indirectly inhibits tyrosine kinases exerted dose-dependent apoptosis-inducing effect on in vitro HT-29 cell culture and reduced tumor mass in mouse xenograft)
IT 122520-86-9, AG213
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG-213 dose-dependently decreased number of cultured HT-29 cells and showed retardation of growth of HT-29 tumor xenograft in mouse)
IT 148741-32-6, AG1007
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1007 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 153150-84-6, AG1112
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1112 had no apoptosis-inducing effect in HT-29 cell culture)
IT 768395-51-3, AG 1317
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1317 showed greater apoptosis-inducing effect in HT-29 cell culture)
IT 204143-16-8, AG1379
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1379 showed less apoptosis-inducing effect in HT-29 cell culture)
IT 169120-22-3, AG 1393
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1393 had no apoptosis-inducing effect in HT-29 cell culture)
IT 71308-34-4, AG 1406
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1406 showed greater apoptosis-inducing effect in HT-29 cell culture)
IT 133550-30-8, AG490
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG490 had no apoptosis-inducing effect in HT-29 cell culture)
IT 133550-34-2, AG555
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG555 had no apoptosis-inducing effect in HT-29 cell culture)
IT 133550-41-1, AG556
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG556 had no apoptosis-inducing effect in HT-29 cell culture)
IT 148741-30-4, AG879
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG879 had no apoptosis-inducing effect in HT-29 cell culture)
IT 768395-53-5, GO 06
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor GO06 showed greater apoptosis-inducing effect in HT-29 cell culture)
IT 768395-55-7, HDL 1122
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL1122 had no apoptosis-inducing effect in HT-29 cell culture)
IT 768395-62-6, HDL 1322
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL1322 showed less apoptosis-inducing effect in HT-29 cell culture)
IT 768396-23-2, HDL 1735
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL1735 showed low apoptosis-inducing effect in HT-29 cell culture)
IT 768396-20-9, HDL 2232

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL2232 had no apoptosis-inducing effect in HT-29 cell culture)

IT 768396-30-1, HDL 2434
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL2434 showed low apoptosis-inducing effect in HT-29 cell culture)

IT 169120-32-5, HDL 2722
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL2722 showed less apoptosis-inducing effect in HT-29 cell culture)

IT 768396-37-8, HDL 2735
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL2735 had no apoptosis-inducing effect in HT-29 cell culture)

IT 768395-95-5, HDL 451
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL451 showed less apoptosis-inducing effect in HT-29 cell culture)

IT 768396-03-8, HDL 622
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL622 had no apoptosis-inducing effect in HT-29 cell culture)

IT 768395-64-8, HDL 624
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL624 showed less apoptosis-inducing effect in HT-29 cell culture)

IT 768395-94-4, HDL 633
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor HDL633 had no apoptosis-inducing effect in HT-29 cell culture)

IT 768396-46-9, OBF 1422
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor OBF1422 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 169120-35-8, OBF 1622
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor OBF1622 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 768396-49-2, OBF 1625
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor OBF1625 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 768396-65-2, OBF 1635
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor OBF1635 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 768396-66-3, OBF 1834
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor OBF1834 showed greater apoptosis-inducing effect in HT-29 cell culture)

IT 768395-54-6, OL 163
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(tyrosine kinase inhibitor OL163 showed greater apoptosis-inducing effect in HT-29 cell culture)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

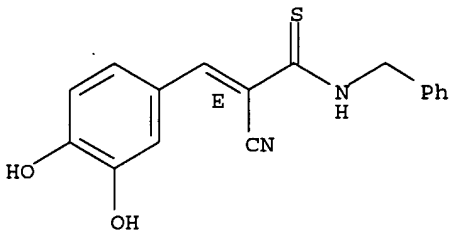
(1) Amin, F; Cell Biol Int 2000, V24, P253 HCAPLUS
(2) Aviv, G; J Med Chem 1996, V39, P4905
(3) Keri, G; Proc Natl Acad Sci USA 1996, V93, P12513 HCAPLUS
(4) Magyar, K; Handb Exp Pharmacol 2000, V142, P457 HCAPLUS
(5) Orfi, L; Bioorg Med Chem 1996, V4(4), P547 HCAPLUS

IT **148741-32-6**, AG1007
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor AG1007 showed greater apoptosis-inducing effect in HT-29 cell culture)

RN 148741-32-6 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:633389 HCAPLUS

DN 139:159929

ED Entered STN: 15 Aug 2003

TI Non-myeloablative tolerogenic treatment with tyrphostins

IN Slavin, Shimon; Morecki, Shoshana; Levitzki, Alexander; Gazit, Aviv

PA **Yissum** Research Development Company of the Hebrew University of Jerusalem, Israel; Hadasit Medical Research Services and Development Ltd.

SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K

CC 1-7 (Pharmacology)
Section cross-reference(s): 15

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003065971	A2	20030814	WO 2002-IL467	20020616
	WO 2003065971	C2	20031120		
	WO 2003065971	A3	20040916		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2450807	AA	20030814	CA 2002-2450807	20020616
	EP 1482983	A2	20041208	EP 2002-738590	20020616

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US	2004197335	A1	20041007	US 2003-479523	20031211
PRAI US	2001-297795P	P	20010614		
WO	2002-IL467	W	20020616		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003065971	ICM	A61K
WO 2003065971	ECLA	A61K031/277; A61K031/277+M; A61K031/404; A61K031/404+M; A61K031/50; A61K031/50+M; A61K031/517; A61K031/517+M; A61K031/519; A61K031/519+M; A61K039/00+M; A61K039/00D5; A61K039/39; A61K041/00; A61K049/00H
US 2004197335	NCL	424/155.100; 424/184.100; 424/277.100
	ECLA	A61K031/277; A61K031/277+M; A61K031/404; A61K031/404+M; A61K031/50; A61K031/50+M; A61K031/517; A61K031/517+M; A61K031/519; A61K031/519+M; A61K039/00+M; A61K039/00D5; A61K039/39; A61K041/00; A61K049/00H

AB A method of inducing immune tolerance in a first mammal to antigens of a second, non-syngeneic, mammal, is disclosed. The method is utilized to minimize graft rejection and/or reduce graft-vs.-host diseases in transplantation procedures and to produce hematopoietic mixed chimeras. Methods of determining the activity of tyrphostins and the optimal concentration thereof in this method are also disclosed.

ST nonmyeloablative tolerogenic treatment tyrphostin

IT Immunosuppressants
(addnl. therapeutic agent; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Lymphocyte
(allogeneic; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(allotransplant; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-leukocyte, as adjuvant immunosuppressive therapy; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Alkylating agents, biological
Radiotherapy
(as adjuvant immunosuppressive therapy; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(bone marrow; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Neoplasm
(cancer patients; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(graft-vs.-host reaction; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Human
Immune tolerance
Immunomodulators
Lymphocyte
T cell (lymphocyte)
Transplant and Transplantation
Transplant rejection
(non-myeloablative tolerogenic treatment with tyrphostins to eliminate

lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(pancreatic islet; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Rattus
Sus scrofa domestica
(production of hematopoietic mixed chimera; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(skin; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Transplant and Transplantation
(small intestine; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Intestine
(small, transplant; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Bone marrow
Hematopoietic precursor cell
Pancreatic islet of Langerhans
Skin
(transplant; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT Cytotoxic agents
(tyrphostins; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

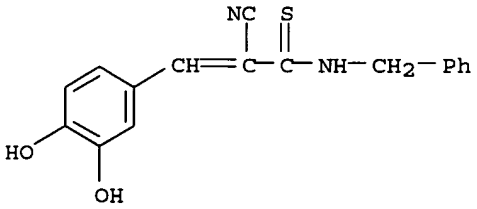
IT Transplant and Transplantation
(xenotransplant; non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT 59-49-4D, 2(3H)-Benzoxazolone, derivs. 62-53-3D, Aniline, derivs. 79-06-1D, Acrylamide, cyano-substituted 91-19-0D, Quinoxaline, derivs. 107-13-1D, Acrylonitrile, derivs. 253-82-7D, Quinazoline, derivs. 37342-64-6D, Pyridone, tricyclic and tetracyclic analogs 40620-23-3D, Thioacrylamide, cyano-substituted 52109-66-7 65678-07-1 71897-07-9 118409-60-2 118409-62-4 134036-52-5 140674-76-6 149092-35-3 149092-50-2 149551-30-4 149551-41-7 167018-37-3 169120-22-3 172889-26-8 172889-27-9 189290-57-1 202475-60-3 204005-46-9 294191-45-0 330161-87-0 577784-43-1 577784-44-2 577784-45-3 577784-46-4 577784-47-5 577784-48-6 577784-49-7 577784-50-0 577784-51-1 577784-52-2 577784-53-3 577784-54-4 577784-55-5 **577784-57-7** 577784-58-8 577784-59-9 577784-60-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

IT **577784-57-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-myeloablative tolerogenic treatment with tyrphostins to eliminate lymphocyte responding to non-syngeneic donor antigens)

RN 577784-57-7 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(9CI) (CA INDEX NAME)



L27 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:509009 HCAPLUS
DN 137:321866
ED Entered STN: 08 Jul 2002
TI Characterization of the in vitro kinase activity of a partially purified soluble GST/JAK2 fusion protein
AU Duhe, Roy J.; Clark, Emily A.; Farrar, William L.
CS Intramural Research Support Program, SAIC -Frederick, Frederick, MD, USA
SO Molecular and Cellular Biochemistry (2002), 236(1&2), 23-35
CODEN: MCBIB8; ISSN: 0300-8177
PB Kluwer Academic Publishers
DT Journal
LA English
CC 7-2 (Enzymes)
AB The biochem. and biophys. characteristics of Janus protein tyrosine kinases (JAKs), which are essential early mediators of cytokine-initiated signal propagation, are virtually undefined. To facilitate the in vitro anal. of JAK-mediated catalysis, we substantially purified a soluble recombinant JAK2 and developed a novel means of quantifying JAK-catalyzed product formation. Glutathione-S-transferase fusion proteins containing active and inactive forms of rat Janus kinase 2 (GST:rJAK2 and GST:rJAK2(CΔ795)) were highly purified via affinity chromatog. A microtiter plate-based ELISA was used to measure tyrosine phosphorylation of a streptavidin-immobilized biotinylated STAT1-derived peptide. The ELISA data indicated that only about 1% of the enzyme was involved in exogenous substrate phosphorylation. Other immobilized peptides served as apparent substrates with varying efficacy. Traditional radioisotopic autokinase assays demonstrated that the activity of the purified fusion protein was inhibited by a variety of tyrphostin inhibitors. Non-radiolabeled adenine nucleotides, but not guanine nucleotides, inhibited the radioisotopic autokinase assay. These observations verify that the catalytic activity of JAK2 is highly regulated, and are consistent with the suggestion that JAK2 may require addnl. accessory proteins, such as a potential upstream regulatory kinase, for full catalytic activity.
ST JAK2 kinase GST fusion autophosphorylation tyrphostin adenine nucleotide
IT Phosphorylation, biological
(autophosphorylation; adenine nucleotide inhibition of autophosphorylation of JAK2 kinase fused with glutathione S-transferase)
IT 58-64-0, 5'-ADP, biological studies 25612-73-1, AMP-PNP 35094-46-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(adenine nucleotide inhibition of autophosphorylation of JAK2 kinase fused with glutathione S-transferase)
IT 152478-57-4DP, JAK2 kinase, fusion with glutathione S-transferase
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(characterization of in vitro kinase activity of a partially purified soluble glutathione S-transferase/JAK2 kinase fusion protein)
IT 50812-37-8D, Glutathione S-transferase, fusion with JAK2 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of in vitro kinase activity of a partially purified soluble glutathione S-transferase/JAK2 kinase fusion protein)
IT 2826-26-8, Tyrphostin A1 118409-58-8, Tyrphostin A 25 133550-32-0,

Tyrphostin B44 134036-52-5, Tyrphostin B42 139087-53-9, Tyrphostin B48 149092-34-2, Tyrphostin B46 149092-35-3, Tyrphostin B56 **227030-50-4**, Tyrphostin B 50
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyrphostin inhibition of autophosphorylation of JAK2 kinase fused with glutathione S-transferase)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

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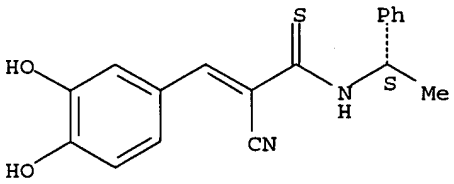
IT **227030-50-4**, Tyrphostin B 50
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyrphostin inhibition of autophosphorylation of JAK2 kinase fused with glutathione S-transferase)

RN 227030-50-4 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-[(1S)-1-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L27 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:901175 HCAPLUS

DN 134:172694

ED Entered STN: 24 Dec 2000
TI Direct Inhibition of the Hexose Transporter GLUT1 by Tyrosine Kinase Inhibitors
AU Vera, Juan Carlos; Reyes, Alejandro M.; Velasquez, Fernando V.; Rivas, Coralia I.; Zhang, Rong Hua; Strobel, Pablo; Slebe, Juan Carlos; Nunez-Alarcon, Juana; Golde, David W.
CS Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SO Biochemistry (2001), 40(3), 777-790
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 13
AB The facilitative hexose transporter GLUT1 is a multifunctional protein that transports hexoses and dehydroascorbic acid, the oxidized form of vitamin C, and interacts with several mols. structurally unrelated to the transported substrates. Here we analyzed in detail the interaction of GLUT1 with a group of tyrosine kinase inhibitors that include natural products of the family of flavones and isoflavones and synthetic compds. such as the tyrphostins. These compds. inhibited, in a dose-dependent manner, the transport of hexoses and dehydroascorbic acid in human myeloid HL-60 cells, in transfected Chinese hamster ovary cells overexpressing GLUT1, and in normal human erythrocytes, and blocked the glucose-displaceable binding of cytochalasin B to GLUT1 in erythrocyte ghosts. Kinetic anal. of transport data indicated that only tyrosine kinase inhibitors with specificity for ATP binding sites inhibited the transport activity of GLUT1 in a competitive manner. In contrast, those inhibitors that are competitive with tyrosine but not with ATP failed to inhibit hexose uptake or did so in a noncompetitive manner. These results, together with recent evidence demonstrating that GLUT1 is a nucleotide binding protein, support the concept that the inhibitory effect on transport is related to the direct interaction of the inhibitors with GLUT1. We conclude that predicted nucleotide-binding motifs present in GLUT1 are important for the interaction of the tyrosine kinase inhibitors with the transporter and may participate directly in the binding transport of substrates by GLUT1.
ST tyrosine kinase inhibitor hexose transporter GLUT1
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GLUT-1 (glucose-transporting, 1); tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT Flavones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isoflavones; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT Structure-activity relationship
(transport-affecting; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT Antitumor agents
(tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT Flavones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT Hexoses
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tyrosine kinase inhibitors direct inhibition of hexose transporter

GLUT1)
IT Cytotoxic agents
(tyrphostins; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 90-19-7, Rhamnetin 117-39-5, Quercetin 446-72-0, Genistein 480-16-0, Morin 480-19-3, IsoRhamnetin 486-66-8, Daidzein 491-80-5, Biochanin a 529-44-2, Myricetin 2826-26-8, Tyrphostin A1 3681-99-0, Puerarin 63177-57-1, Methyl 2,5-dihydroxycinnamate 118409-57-7, Tyrphostin A23 118409-58-8, Tyrphostin A 25 118409-59-9, Tyrphostin A46 125697-91-8, Lavendustin b 125697-92-9, Lavendustin a 133550-32-0, Tyrphostin B44 139087-53-9, Tyrphostin B48 149092-34-2, Tyrphostin B46 149092-35-3, Tyrphostin B56
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 56-65-5, Atp, biological studies 61-90-5, Leucine, biological studies 146-72-5, 3-O-Methylglucose 154-17-6, 2-Deoxyglucose 490-83-5, Dehydroascorbic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 80449-02-1, Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 118409-60-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin A47; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 126433-07-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin A51; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 5553-97-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin A63; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 148741-30-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin AG 879; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
IT 227030-50-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin B 50; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)
RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD
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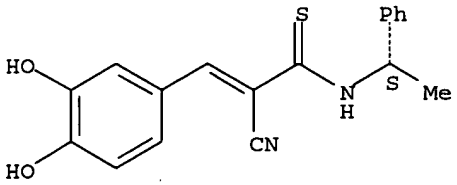
IT **227030-50-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrphostin B 50; tyrosine kinase inhibitors direct inhibition of hexose transporter GLUT1)

RN 227030-50-4 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-[(1S)-1-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L27 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:828028 HCAPLUS
DN 134:127813
ED Entered STN: 28 Nov 2000
TI Substrate Competitive Inhibitors of IGF-1 Receptor Kinase
AU Blum, Galia; Gazit, Aviv; Levitzki, Alexander
CS Department of Biological Chemistry, Alexander Silberman Institute of Life Sciences Department of Organic Chemistry, Institute of Chemistry The Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SO Biochemistry (2000), 39(51), 15705-15712
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-8 (Enzymes)
Section cross-reference(s): 1
AB IGF-1 and its receptor play a pivotal role in many cancers, and therefore, IGF-1R is an attractive target for the design of inhibitors. In this communication, we report on a number of lead compds. for inhibitors of the isolated IGF-1R kinase. The search for these compds. utilized two novel in vitro assays and was aided by the knowledge of the three-dimensional structure of the insulin receptor kinase domain, which is 84% homologous to the IGF-1R kinase domain. The most potent inhibitor found in these assays was tyrphostin AG 538, with an IC50 = 400 nM. In computer modeling, AG 538 was placed in the kinase domain of the insulin receptor and was able to sit in place of tyrosines 1158 and 1162, which undergo autophosphorylation. Exptl. it is indeed found that AG 538 does not compete with ATP but competes with the IGF-1R substrate. We prepared I-OMe AG 538, which is more hydrophobic and less sensitive to oxidation than AG 538. Both AG 538 and I-OMe AG 538 inhibit IGR-1R autophosphorylation in intact cells in a dose-dependent manner but I-OMe-AG 538 is superior, probably because of its enhanced hydrophobic nature. Both compds. inhibit the activation of the downstream targets PKB and Erk2. These findings suggest that AG 538 and I-OMe-AG 538 can serve as a lead compound for the development of substrate competitive inhibitors of the IGF-1R. The possible advantage of substrate competitive inhibitors vis-a-vis ATP competitive inhibitors is discussed.
ST IGF 1 receptor kinase inhibitor prepn; structure activity IGF receptor kinase inhibitor; enzyme inhibition assay IGF receptor kinase
IT Signal transduction, biological
(IGF-1 receptor signaling; substrate competitive inhibitors of IGF-1 receptor kinase)
IT Phosphorylation, biological
(autophosphorylation; substrate competitive inhibitors of IGF-1 receptor kinase)
IT Insulin-like growth factor I receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrate competitive inhibitors of IGF-1 receptor kinase)
IT 79079-06-4, EGF-receptor kinase 88201-45-0, Insulin receptor kinase 141349-89-5, Src kinase 148640-14-6, Protein kinase B
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition; substrate competitive inhibitors of IGF-1 receptor kinase)
IT 4722-81-0, AG 1693 6623-89-8, AG 242 26195-45-9, AG 1049 65678-07-1, AG 1024 71308-34-4, AG 1406 116313-73-6, AG 1288 118409-54-4, AG 34 118409-57-7, AG 18 118409-58-8, AG 82 122520-85-8, AG 99

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321996-63-8, AG 1668 321996-64-9, AG 251 321996-65-0, AG 252
321996-66-1, AG 1694 321996-67-2, AG 2101 321996-69-4, AG 1501
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(substrate competitive inhibitors of IGF-1 receptor kinase)

IT 103843-29-4, Insulin-like growth factor-I receptor kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(substrate competitive inhibitors of IGF-1 receptor kinase)

IT 67763-96-6, Insulin-like growth factor I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrate competitive inhibitors of IGF-1 receptor kinase)

IT 107-95-9, β-Alanine 5438-36-8, 5-Iodovanillin 56961-48-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(substrate competitive inhibitors of IGF-1 receptor kinase)

IT 321919-12-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(substrate competitive inhibitors of IGF-1 receptor kinase)

IT 321919-11-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(substrate competitive inhibitors of IGF-1 receptor kinase)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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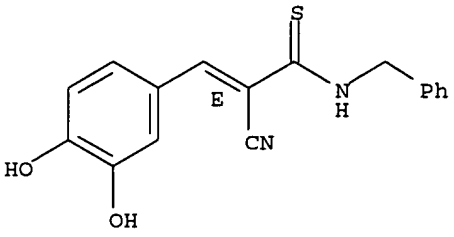
(34) Yaish, P; Science 1988, V242, P933 HCAPLUS
IT **148741-32-6**, AG 1007
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(substrate competitive inhibitors of IGF-1 receptor kinase)
RN 148741-32-6 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:608546 HCAPLUS
DN 133:198419
ED Entered STN: 01 Sep 2000
TI Reduction of hair growth by tyrosine kinase inhibitors
IN Henry, James P.; Ahluwalia, Gurpreet S.
PA The Gillette Company, USA
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K007-06
ICS A61K031-135; A61K031-215; A61K031-395; A61K031-425; A61K031-275
CC 62-4 (Essential Oils and Cosmetics)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000050002	A1	20000831	WO 2000-US4198	20000218
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6121269	A	20000919	US 1999-255063	19990222
	CA 2360524	AA	20000831	CA 2000-2360524	20000218
	BR 2000008239	A	20011106	BR 2000-8239	20000218
	EP 1156775	A1	20011128	EP 2000-914636	20000218
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AU 776167	B2	20040826	AU 2000-35999	20000218
PRAI	US 1999-255063	A1	19990222		
	WO 2000-US4198	W	20000218		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000050002	ICM	A61K007-06
	ICS	A61K031-135; A61K031-215; A61K031-395; A61K031-425; A61K031-275

US 6121269 NCL 424/401.000; 514/295.000; 514/415.000; 514/520.000; 514/535.000; 514/567.000; 514/629.000

AB Mammalian hair growth is reduced by applying to the skin an inhibitor of protein-tyrosine kinase. A method is described for applying to the skin a composition including an inhibitor of protein-tyrosine kinases in an amount effective to reduce hair growth. The unwanted hair growth which is reduced may be normal hair growth, or hair growth that results from an abnormal or diseased condition. The preferred composition includes at least one inhibitor of protein-tyrosine kinase in a cosmetically and/or dermatol. acceptable vehicle. The composition may be a solid, semi-solid, or liquid The composition may be, for example, a cosmetic and dermatol. product in the form of an, for example, ointment, lotion, foam, cream, gel, or hydroalcoholic solution The composition may also be in the form of a shaving preparation or an aftershave. Human hair follicle growth assays showed that tyrphostin A48, erbstatin, lavendustin A, Me caffeate, and tyrphostin AG1478 showed the inhibition rate of 40-100 %.

ST tyrosine kinase inhibitor hair growth redn

IT Shaving preparations
(aftershave; hair growth inhibition by tyrosine kinase inhibitors)

IT Cosmetics
(depilatories; hair growth inhibition by tyrosine kinase inhibitors)

IT Cosmetics
Hirsutism
Shaving preparations
(hair growth inhibition by tyrosine kinase inhibitors)

IT Epidermal growth factor receptors
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(hair growth inhibition by tyrosine kinase inhibitors)

IT 80449-02-1, Tyrosine kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hair growth inhibition by tyrosine kinase inhibitors)

IT 127-35-5, Phenazocine 3785-90-8, 4-Hydroxybenzylidenemalononitrile 3843-74-1, Methyl caffeate 10083-24-6, Piceatannol 10537-47-0 70563-58-5, Herbimycin A 100827-28-9, Erbstatin 118409-57-7 118409-58-8 118409-59-9 118409-60-2, Tyrphostin A 47 125697-92-9, Lavendustin A 126433-07-6, Tyrphostin A51 133550-32-0 134036-52-5 134036-53-6 139087-53-9 140674-76-6 144978-82-5 149092-34-2 149092-35-3 149092-50-2 153436-53-4, Tyrphostin AG 1478 168135-79-3 **227030-50-4**, Tyrphostin B 50
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(hair growth inhibition by tyrosine kinase inhibitors)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Handelman; WO 9609806 A 1996 HCAPLUS

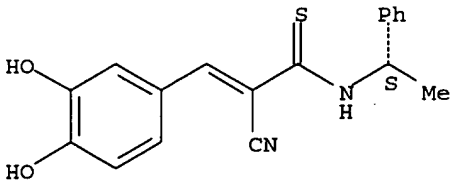
(2) Unilever Plc; EP 0403238 A 1990 HCAPLUS

IT **227030-50-4**, Tyrphostin B 50
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(hair growth inhibition by tyrosine kinase inhibitors)

RN 227030-50-4 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-[(1S)-1-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L27 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:586601 HCAPLUS
DN 133:275853
ED Entered STN: 24 Aug 2000
TI QSAR development to describe HIV-1 integrase inhibition
AU Yuan, H.; Parrill, A. L.
CS Department of Chemistry, University of Memphis, Memphis, TN, 38152, USA
SO THEOCHEM (2000), 529, 273-282
CODEN: THEODJ; ISSN: 0166-1280
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-3 (Pharmacology)
AB HIV-1 integrase(IN) is one of three viral enzymes required for replication. IN mediates integration of viral DNA into the host genome in two steps: 3'-processing and strand transfer. It is currently recognized as an important target for therapeutic development against AIDS. QSAR (Quant. Structure-Activity Relationship) modeling was utilized to study HIV-1 integrase inhibition. QSAR models were constructed to predict the IC50 values for the two structural classes (salicyhydrazines and tyrphostins) independently and in combination. The results showed that the models for different structural classes have different dependence on the same descriptors. It suggests that salicylhydrazines and tyrphostins might have different binding sites in HIV-1 integrase.
ST salicyhydrazine tyrphostin structure activity HIV1 integrase; antiviral antiAIDS QSAR salicyhydrazine tyrphostin integrase
IT Anti-AIDS agents
Human immunodeficiency virus 1
(QSAR development to describe HIV-1 integrase inhibition)
IT Structure-activity relationship
(antiviral; QSAR development to describe HIV-1 integrase inhibition)
IT 23647-78-1, NSC 408200 77869-95-5, NSC 652177 87444-06-2, NSC 653029 87444-08-4, NSC 653035 118409-58-8, AG 82 124814-38-6, NSC 652178 133550-18-2, AG 538 133550-30-8, AG 490 133550-34-2, AG 555 133550-41-1, AG 556 136273-05-7, AG 1233 140674-77-7, AG 537 **148741-32-6**, AG 1007 158081-87-9, AG 946 167493-18-7, AG 1292 168835-85-6, AG 550 170448-92-7, AG 1387 170449-22-6, AG 1075 171674-65-0, AG 575 171674-66-1, AG 638 171674-68-3, AG 588 171674-69-4, AG 589 171674-70-7, AG 590 171674-71-8, AG 1136 171674-72-9, AG 591 171674-73-0, AG 593 171674-75-2, AG 982 171674-76-3, AG 1717 171674-79-6, AG 1093 171674-80-9, AG 921 171674-82-1, AG 1661 171674-83-2, AG 822 173075-24-6, AG 1718 193014-71-0, NSC 652173 213010-81-2, NSC 653039 213010-83-4, NSC 652174 213010-84-5, NSC 652175 213010-85-6, NSC 652176 213010-86-7, NSC 652179 213010-87-8, NSC 652180 213010-88-9, NSC 652182 213010-89-0, NSC 652181
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR development to describe HIV-1 integrase inhibition)
IT 52350-85-3, Integrase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(QSAR development to describe HIV-1 integrase inhibition)
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
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(17) Robinson, W; Infect Med 1998, V15, P129
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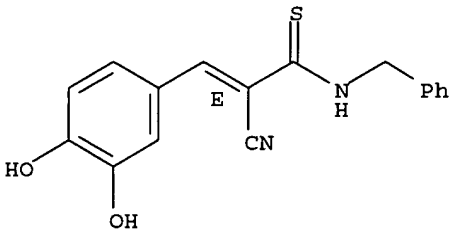
IT **148741-32-6**, AG 1007
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR development to describe HIV-1 integrase inhibition)
RN 148741-32-6 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:179247 HCAPLUS
DN 131:27533
ED Entered STN: 19 Mar 1999
TI Tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line in vitro
AU Twaddle, George M.; Turbov, Jane; Liu, Naxin; Murthy, Satya
CS Cell Biology Laboratory, Departments of Surgery and Medicine, Evanston Hospital, Evanston, IL, USA
SO Journal of Surgical Oncology (1999), 70(2), 83-90
CODEN: JSONAU; ISSN: 0022-4790
PB Wiley-Liss, Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Receptor tyrosine kinase (RTK) activation is critical for growth factor-mediated cell proliferation. Blockade of RTK activation inhibits growth factor-induced cell proliferation. A panel of RTK inhibitors (tyrphostins) have been tested and compared for their antiproliferative effects on the hormone-dependent human breast cancer cell line, MCF-7, in vitro. MCF-7 cells (104/well) were seeded into 96 well plates and maintained in DMEM with 1% bovine serum albumin (BSA), 200-pg/mL estrogen, or 10% fetal bovine serum. After a defined time interval, the cells were exposed to RTK inhibitors and a non-RTK-inhibitory analog of tyrphostins

(0 to 400 μM). After 3 days, the number of viable cells in each well was estimated by an MTT assay and the results expressed as percent of controls. Using a representative tyrphostin, A47, the validity of MTT assay as a measure of cell proliferation was tested by a colony formation assay and by immunostaining with Ki-67 antibodies. MCF-7 cells maintained in DMEM containing 1% BSA without E2 or serum showed a minimal increase in cell number Supplementation with E2 stimulated cell proliferation in a dose-dependent manner. This E2-mediated growth stimulation was completely inhibited (cytostatic effects) by the epidermal growth factor receptor (EGFR)-selective tyrphostins A47, B48, RG13022, and B50. These same tyrphostins also decreased the cell nos. to below control nos. in cultures maintained in 1% BSA or in serum containing medium (cytostatic/cytotoxic effects). B44 (EGFR-selective tyrphostin), AG1295 (platelet-derived growth factor receptor [PDGFR]-selective tyrphostin), and A1 had no inhibitory effects on cells with or without E2 treatments. However, A1 inhibited cell growth under serum supplementation. Genistein, a phytoestrogen, stimulated the autonomous, E2-induced as well as serum-induced growth of MCF-7 cells. Cell proliferation results derived from the MTT assay were corroborated by both the colony formation assay as well as the Ki-67 assay. Of the agents tested, only EGFR-selective tyrphostins blocked E2-stimulated tumor cell proliferation, as opposed to the PDGFR-selective tyrphostin, RTK noninhibitory agent, or the phytoestrogen, genistein, which did not exert such an effect. These findings suggest that epidermal growth factor (EGF) is an important mediator of E2-induced proliferation of MCF-7 cells. Thus, tyrphostins may be selectively used to prevent the growth of hormone-dependent breast cancers, particularly re-growth of residual tumor in postmenopausal breast cancer survivors receiving estrogen replacement therapy.

ST tyrosine kinase inhibitor estrogen breast antitumor; tyrphostin estrogen breast antitumor

IT Antitumor agents
(mammary gland; tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT Mammary gland
Mammary gland
(neoplasm, inhibitors; tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT Menopause
(postmenopause; tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT Estrogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT Cytotoxic agents
(tyrphostins; tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT 80449-02-1, Tyrosine kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT 446-72-0, Genistein 2826-26-8, Tyrphostin A1 71897-07-9, AG1295 118409-60-2, Tyrphostin A 47 133550-32-0, Tyrphostin B 44 139087-53-9, Tyrphostin B48 149286-90-8, RG13022 227030-50-4, Tyrphostin B 50
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)

IT 62229-50-9, Epidermal growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tyrosine kinase inhibitors as antiproliferative agents against an

estrogen-dependent breast cancer cell line)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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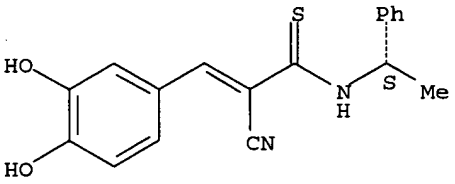
(33) Yoneda, T; Cancer Res 1991, V51, P4430 HCAPLUS
IT **227030-50-4**, Tyrphostin B 50
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line)
RN 227030-50-4 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-[(1S)-1-phenylethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L27 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:400243 HCAPLUS
DN 129:156456
ED Entered STN: 01 Jul 1998
TI Inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase
AU Kleinberger-Doron, Nurit; Shelah, Noa; Capone, Ricardo; Gazit, Aviv;

Levitzki, Alexander
CS Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SO Experimental Cell Research (1998), 241(2), 340-351
CODEN: ECREAL; ISSN: 0014-4827
PB Academic Press
DT Journal
LA English
CC 1-3 (Pharmacology)
AB The authors have previously reported that certain tryphostins which block EGF-R phosphorylation in cell-free systems fail to do so in intact cells. Nevertheless, the authors found that this family of tyrphostins inhibits both EGF- and calf serum-induced cell growth and DNA synthesis [Osherov, N.A., Gazit, C., Gilon, and Levitzki, A. (1993). Selective inhibition of the EGF and HER2/Neu receptors by Tyrphostins. J. Biol. Chemical 268, 11134-11142.]; now the authors show that these tryphostins exert their inhibitory activity even when added at a time when the cells have already passed their restriction point and receptor activation is no longer necessary. AG555 and AG556 arrest 85% of the cells at late G1, whereas AG490 and AG494 cause cells to arrest at late G1 and during S phase. No arrest occurs during G2 or M phase. Further anal. revealed that these tyrphostins act by inhibiting the activation of the enzyme Cdk2 without affecting its levels or its intrinsic kinase activity. Furthermore, they do not alter the association of Cdk2 to cyclin E or cyclin A or to the inhibitory proteins p21 and p27. These compds. also have no effect on the activating phosphorylation of Cdk2 by Cdk2 activating kinase (CAK) and no effect on the catalytic domain of cdc25 phosphatase. These compds. lead to the accumulation of phosphorylated Cdk2 on tyrosine 15 which is most probably the cause for its inhibition leading to cell cycle arrest at G1/S. A structure-activity relation study defines a very precise pharmacophore, suggesting a unique mol. target not yet identified and which is most probably involved in the regulation of the tyrosine-phosphorylated state of Cdk2. These compds. represent a new class of cell proliferation blockers whose target is Cdk2 activation. (c) 1998 Academic Press.
ST Cdk2 kinase tyrphostin cell cycle arrest; antiproliferative agent tyrphostin structure Cdk2 kinase
IT Structure-activity relationship
(cell cycle arrest-inducing; inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)
IT Cell cycle
Cytotoxic agents
(inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)
IT Proliferation inhibition
(proliferation inhibitors; inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)
IT Phosphorylation, biological
(protein, of tyrosine; inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)
IT Cytotoxic agents
(tyrphostins; inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)
IT 122520-86-9, AG213 133550-30-8, AG490 133550-34-2, AG555
133550-35-3, AG494 133550-41-1, AG 556 133550-44-4, AG 675
148741-32-6, AG 1007 153436-53-4, AG1478 168835-82-3, AG 1498
170448-92-7, AG 1387 170449-11-3, AG 1580 171674-83-2, AG 822
211178-63-1, AG 1516 211178-64-2, AG 493 211178-65-3, AG 1581
211178-66-4, AG 1505 211178-67-5, AG 527 211178-68-6, AG 1664
211178-69-7, AG 1659 211178-70-0, AG 1146 211178-71-1, AG 1106
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)

IT 141349-86-2, Cdk2 kinase 141349-86-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

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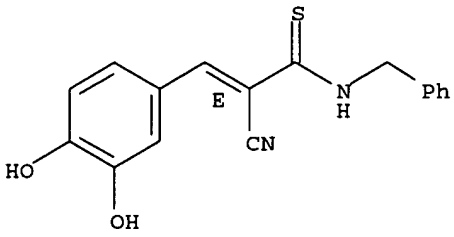
IT **148741-32-6**, AG 1007
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)

RN 148741-32-6 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

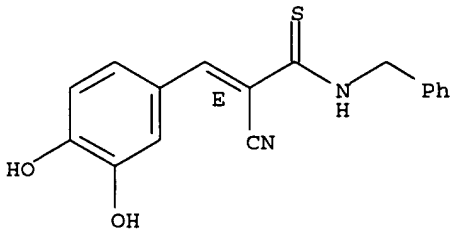
Double bond geometry as shown.



L27 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:116898 HCAPLUS
DN 124:249905
ED Entered STN: 24 Feb 1996
TI Inhibition of acute lymphoblastic leukemia by a Jak-2 inhibitor
AU Meydan, Naftaly; Grunberger, Tom; Dadi, Harjit; Shahar, Michal; Arpaia, Enrico; Lapidot, Zvi; Leeder, J. Steven; Freedman, Melvin; Cohen, Amos; et al.
CS The Hospital for Sick Children, Univ. Toronto, Toronto, M5G 1X8, Can.
SO Nature (London) (1996), 379(6566), 645-8
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. Despite the progress achieved in its treatment, 20% of cases relapse and no longer respond to chemotherapy. The most common phenotype of all cells share surface antigens with very early precursors of B cells and are therefore believed to originate from this lineage. Characterization of the growth requirement of ALL cells indicated that they were dependent on various cytokines, suggesting paracrine and/or autocrine growth regulation. Because many cytokines induce tyrosine phosphorylation in lymphoid progenitor cells, and constitutive tyrosine phosphorylation is commonly observed in B-lineage leukemias, attempts have been made to develop protein tyrosine kinase (PTK) blockers of leukemia cell growth. Here the authors show that leukemic cells from patients in relapse have constitutively activated Jak-2 PTK. Inhibition of Jak-2 activity by a specific tyrosine kinase blocker, AG-490, selectively blocks leukemic cell growth in vitro and in vivo by inducing programmed cell death, with no deleterious effect on normal hematopoiesis. None of the other tyrphostins tested had any activity against leukemic cells.
ST leukemia Jak2 protein tyrosine kinase inhibitor; AG490 leukemia Jak2 protein tyrosine kinase; tyrphostin leukemia inhibitor Jak2 protein kinase
IT Neoplasm inhibitors
(acute lymphocytic leukemia, inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)
IT 71897-07-9, AG 1295 118409-57-7, AG 18 118409-62-4, AG 126
122520-79-0, AG 30 122520-91-6, AG 294 133550-30-8, AG 490
134036-53-6, AG 370 148741-30-4, AG 879 **148741-32-6**, AG 1007
153150-84-6, AG 1112 153436-53-4, AG 1478 175178-83-3, AG 574
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)
IT 152478-57-4, Jak-2 protein tyrosine kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)
IT **148741-32-6**, AG 1007

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)
RN 148741-32-6 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:897080 HCAPLUS
DN 124:105560
ED Entered STN: 04 Nov 1995
TI Effects of Tyrphostins, Protein Kinase Inhibitors, on Human Immunodeficiency Virus Type 1 Integrase
AU Mazumder, Abhijit; Gazit, Aviv; Levitzki, Alexander; Nicklaus, Marc; Yung, Jessie; Kohlhagen, Glenda; Pommier, Yves
CS Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, 20892, USA
SO Biochemistry (1995), 34(46), 15111-22
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 7
AB Efficient replication of HIV-1 requires establishment of the proviral state, i.e., the integration of a DNA copy of the viral genome, synthesized by reverse transcriptase, into a chromosome of the host cell. Integration is catalyzed by the viral integrase protein. The authors have previously reported that phenolic moieties in compds. such as naphthoquinones, flavones, caffeic acid phenethyl ester (CAPE), and curcumin confer inhibitory activity against HIV-1 integrase. The authors have extended these findings by examining the effects of tyrphostins, tyrosine kinase inhibitors. The catalytic activities of HIV-1 integrase and the formation of enzyme-DNA complexes using photocross-linking were examined Both steps of the integration reaction, 3'-processing and strand transfer, were inhibited by tyrphostins at micromolar concns. The DNA binding activity of integrase was inhibited at higher concns. of tyrphostins. Disintegration, an apparent reversal of the strand transfer reaction, catalyzed by an integrase mutant lacking the N-terminal zinc finger and C-terminal DNA binding domains is also inhibited by tyrphostins, indicating that the binding site for these compds. resides in the central catalytic core of HIV-1 integrase. Binding of tyrphostins at or near the integrase catalytic site was also suggested by expts. showing a global inhibition of the choice of attacking nucleophile in the 3'-processing reaction. None of the tyrphostins tested inhibited eukaryotic topoisomerase I, even at 100 μM, suggesting selectivity for integrase inhibition. Mol.-modeling studies have revealed that, after energy minimization, several tyrphostins may adopt folded conformations. The similarity of the tyrphostin family to other families of inhibitors is discussed. Tyrphostins may provide lead compds. for development of novel

antiviral agents for the treatment of acquired immunodeficiency syndrome based upon inhibition of HIV-1 integrase.

ST tyrphostin HIV integrase

IT Molecular structure-biological activity relationship
Virucides and Virustats
(effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

IT Deoxyribonucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(formation of enzyme-DNA complexes; effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

IT Virus, animal
(human immunodeficiency 1, effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

IT 171674-76-3P, AG 1717
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

IT 118409-58-8, Ag 82 133550-18-2, AG 538 133550-30-8, AG 490
133550-34-2, AG 555 133550-41-1, AG 556 136273-05-7, AG 1233
140674-77-7, AG 537 **148741-32-6**, AG 1007 158081-87-9, AG 946
167493-18-7, AG 1292 168835-85-6, AG 550 170448-92-7, AG 1387
170449-22-6, AG 1075 171674-65-0, AG 575 171674-66-1, AG 638
171674-67-2, AG 542 171674-68-3, AG 588 171674-69-4, AG 589
171674-70-7, AG 590 171674-71-8, AG 1136 171674-72-9, AG 591
171674-73-0, AG 593 171674-74-1, AG 592 171674-75-2, AG 982
171674-79-6, AG 1093 171674-80-9, AG 921 171674-82-1, AG 1661
171674-83-2, AG 822 171674-84-3, AG 954 173075-23-5, AG 775
173075-24-6, AG 1718
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

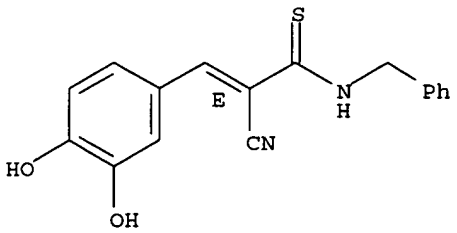
IT 52350-85-3, Integrase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

IT **148741-32-6**, AG 1007
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase)

RN 148741-32-6 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:849326 HCAPLUS
DN 123:246818
ED Entered STN: 12 Oct 1995
TI Compounds for the treatment of disorders related to vasculogenesis and/or angiogenesis
IN Gazit, Aviv; Levitzki, Alexander; App, Harald; Tang, Cho Peng; Mcmahon, Gerald M.
PA **Sugen**, Inc., USA; **Yissum** Research Development Company of the Hebrew University
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-24
ICS A61K031-42; A61K031-275; A61K031-415; A61K031-495; C07C211-45; C07C255-01; C07D209-18; C07D231-38; C07D241-36; C07D265-34; C07D471-02; G01N033-567
CC 1-6 (Pharmacology)
Section cross-reference(s): 25, 28
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9521613	A1	19950817	WO 1995-US1751	19950209
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6177401	B1	20010123	US 1994-193829	19940209
	AU 9518423	A1	19950829	AU 1995-18423	19950209
	EP 748219	A1	19961218	EP 1995-910239	19950209
	EP 748219	B1	20050406		
	R: DE, FR, GB				
	JP 09508642	T2	19970902	JP 1995-521376	19950209
	JP 3202238	B2	20010827		
PRAI	US 1994-193829	A	19940209		
	US 1992-975750	B2	19921113		
	US 1993-38596	B2	19930326		
	WO 1995-US1751	W	19950209		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9521613	ICM	A61K031-24
	ICS	A61K031-42; A61K031-275; A61K031-415; A61K031-495; C07C211-45; C07C255-01; C07D209-18; C07D231-38; C07D241-36; C07D265-34; C07D471-02; G01N033-567
WO 9521613	ECLA	A61K031/235; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; G01N033/50D2B; G01N033/68V
US 6177401	NCL	514/001.000; 435/007.200; 436/501.000; 530/350.000; 530/399.000
	ECLA	A61K031/235; A61K031/275; A61K031/277; A61K031/38; A61K031/40; A61K031/415; A61K031/42; A61K031/495; A61K031/502; A61K031/505; A61K031/517; A61K031/535; C07C229/60; C07C255/36; C07C255/40; C07C255/41; C07C255/66; C07C317/46; C07C327/44; C07D209/18; C07D239/93; C07D239/94; C07D241/42; C07D241/44; C07D487/04+239C+235C; C07D498/04+265C+239C; C07K014/71;

C07K016/28G; G01N033/50D2; G01N033/50D2B; G01N033/68V

OS MARPAT 123:246818

AB The present invention relates to organic mols. capable of modulating tyrosine kinase signal transduction and particularly KDR/FLK-1 receptor signal transduction in order to regulate and/or modulate vasculogenesis and angiogenesis. The invention is based, in part, on the demonstration that KDR/FLK-1 tyrosine kinase receptor expression is associated with endothelial cells and the identification of vascular endothelial growth factor (VEGF) as the high affinity ligand of FLK-1. These results indicate a major role for KDR/FLK-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that express FLK-1 and the use of expressed FLK-1 to evaluate and screen for drugs and analogs of VEGF involved in FLK-1 modulation by either agonist or antagonist activities is also described. The invention also relates to the use of the disclosed compds. in the treatment of disorders, including cancer, diabetes, hemangioma and Kaposi's sarcoma, which are related to vasculogenesis and angiogenesis.

ST angiogenesis compd treatment; vasculogenesis compd treatment; quinoxaline deriv angiogenesis vasculogenesis; quinazoline deriv angiogenesis vasculogenesis; acrylonitrile deriv angiogenesis vasculogenesis

IT Blood vessel
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vascular endothelial growth factor, gene KDR, compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 75706-12-6, Leflunomide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 3458-44-4P 133550-18-2P 140674-76-6P 143993-61-7P 148741-30-4P
148741-31-5P 155566-32-8P 168835-80-1P 168835-81-2P 168835-82-3P
168835-83-4P 168835-84-5P 168835-85-6P 168835-86-7P
168835-87-8P 168835-88-9P 168835-89-0P 168835-90-3P
168835-91-4P 168835-92-5P 168835-93-6P 168835-94-7P 168835-95-8P
168835-96-9P 168835-97-0P 168835-98-1P 168835-99-2P 168836-00-8P
168836-01-9P 168836-02-0P 168836-03-1P 168836-04-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 95-76-1, 3,4-Dichloroaniline 99-40-1 100-46-9, Benzylamine, reactions
106-40-1, p-Bromoaniline 106-45-6, Benzenethiol, 4-methyl- 107-95-9, β-Alanine 108-42-9 109-77-3, Malononitrile 123-08-0 139-85-5, 3,4-Dihydroxybenzaldehyde 298-12-4, Glyoxalic acid 491-36-1, 4(1H)-Quinazolinone 540-37-4, p-Iodoaniline 591-27-5 626-01-7, 3-Iodoaniline 771-97-1, 2,3-Naphthalenediamine 1074-12-0, Phenylglyoxal 1196-69-6, 5-Formylindole 1620-98-0 1960-77-6, Acetamide, 2-cyano-N-[3-(trifluoromethyl)phenyl]- 2078-54-8, 2,6-Diisopropylphenol 2740-81-0, 2-Chlorophenyl isothiocyanate 2941-78-8, 2-Amino-5-methylbenzoic acid 3171-45-7, 4,5-Dimethyl-1,2-benzenediamine 3216-88-4 5438-36-8, 5-Iodovanillin 5653-40-7, 2-Amino-4,5-dimethoxybenzoic acid 5875-28-5, Thiocyanatoacetamide 10412-93-8, N-Benzylcyanoacetamide 16414-34-9, 5-Bromo-3,4-dihydroxybenzaldehyde 28888-44-0, 6,7-Dimethoxy-2,4-quinazolinedione 37463-94-8, Sulfonyldiacetonitrile 133550-33-1, Acetamide, 2-cyano-N-(3-phenylpropyl)- 133550-57-9 168836-05-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 5190-68-1P, 4-Chloroquinazoline 10537-86-7P, 3,5-Diisopropyl-4-hydroxybenzaldehyde 13790-39-1P, 4-Chloro-6,7-dimethoxyquinazoline 13794-72-4P, 4(3H)-Quinazolinone, 6,7-dimethoxy 19181-53-4P,

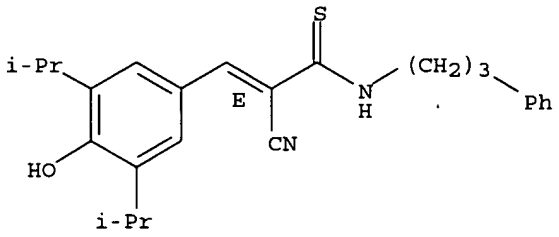
4(1H)-Quinazolinone, 6-methyl- 27389-84-0P 27631-29-4P, 2,4-Dichloro-6,7-dimethoxyquinazoline 28082-82-8P, 2(1H)-Quinoxalinone, 6,7-dimethyl- 29067-81-0P, Quinoxaline, 2-chloro-6,7-dimethyl- 54711-21-6P 58421-79-7P, 4-Chloro-6-methylquinazoline 70071-08-8P 168835-78-7P 168835-79-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT 80449-02-1, Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signal transduction; compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

IT **168835-87-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compds. for the treatment of disorders related to vasculogenesis and/or angiogenesis)

RN 168835-87-8 HCAPLUS
CN 2-Propenethioamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:462816 HCAPLUS
DN 119:62816
ED Entered STN: 21 Aug 1993
TI The tyrosine kinase inhibitor tyrphostin blocks the cellular actions of nerve growth factor
AU Ohmichi, Masahide; Pang, Long; Ribon, Vered; Gazit, Aviv; Levitzki, Alexander; Saltiel, Alan R.
CS Sch. Med., Univ. Michigan, Ann Arbor, MI, 48109, USA
SO Biochemistry (1993), 32(17), 4650-8
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
CC 1-11 (Pharmacology)
AB A series of the synthetic protein kinase inhibitors known as tyrphostins were examined for their effects on the tyrosine autophosphorylation of the ppl40c-trk, nerve growth factor (NGF) receptor. One of the tyrphostins, AG879, inhibited NGF-dependent ppl40c-trk tyrosine phosphorylation, but did not effect tyrosine phosphorylation of epidermal growth factor or platelet-derived growth factor receptors. In addition, the tyrosine phosphorylation of the receptor-associated protein pp38 was also attenuated by the tyrphostin. This effect was time and dose dependent, although inhibition of pp38 phosphorylation occurred earlier and at lower concns. of the compound AG879 also inhibited NGF-induced PLC-γ1 phosphorylation, phosphatidylinositol-3 (PI3) kinase activation, the association of the tyrosine-phosphorylated proteins pp100 and pp110 with the p85 subunit of PI-3 kinase, mitogen activated protein and raf-1 kinases, and c-fos induction. In addition, AG879 inhibited NGF-induced neurite outgrowth in PC12 cells. These data indicate that tyrosine kinase

activity of the pp140c-trk NGF receptor is essential for the cellular actions of this growth factor.

ST tyrphostin AG879 nerve growth factor receptor

IT Phosphorylation, biological
(of tyrosine of nerve growth factor receptor, tyrosine kinase inhibitor tyrphostins effects on)

IT Proteins, specific or class
RL: BIOL (Biological study)
(tyrosine-phosphorylated, nerve growth factor receptor-associated, tyrphostin effect on)

IT Receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nerve growth factor, tyrosine kinase activity of, tyrphostins inhibition of, cellular actions in relation to)

IT Cytotoxic agents
(tyrphostins, preparation of, as tyrosine kinase inhibitor, nerve growth factor cellular action response to)

IT Gene, animal
RL: BIOL (Biological study)
(c-fos, expression of, nerve growth factor stimulation of tyrphostin inhibition of)

IT 80449-02-1, Tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, tyrphostins, cellular action of nerve growth factor blockade of)

IT 9026-43-1, Protein kinase
RL: BIOL (Biological study)
(phosphorylation of, nerve growth factor stimulation of, tyrphostin inhibition of)

IT 60-18-4, Tyrosine, biological studies
RL: BIOL (Biological study)
(phosphorylation of, of nerve growth factor receptor, tyrosine kinase inhibitor tyrphostins effect on)

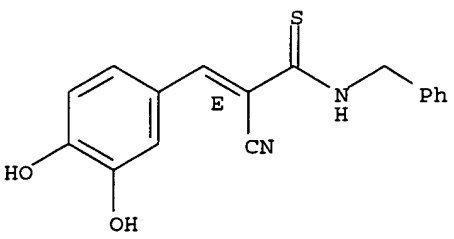
IT 26195-45-9P, AG 1049 65678-07-1P, AG 1024 71308-35-5P, AG17
118409-54-4P, AG 34 118409-57-7P, AG 18 118409-62-4P, AG126
133550-43-3P, AG 561 133550-49-9P, AG 528 148741-30-4P, AG 879
148741-31-5P, AG 974 **148741-32-6P**, AG 1007 148741-33-7P, AG 1034
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as tyrosine kinase inhibitor, nerve growth factor cellular action response to)

IT **148741-32-6P**, AG 1007
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as tyrosine kinase inhibitor, nerve growth factor cellular action response to)

RN 148741-32-6 HCAPLUS

CN 2-Propenethioamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



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